American Journal of Obstetrics and Gynecology

VOL. 69 FEBRUARY, 1955 NO. 2

Transactions of the Society of Obstetricians and Gynaecologists of Canada

INDUCTION OF LABOR, INDICATIONS AND METHODS*

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THE subject of induction of labor has undergone many changes during the last two or three decades, both in the indications for the premature interruption of pregnancy and in the methods employed for bringing about premature labor.

The artificial termination of pregnancy has been practiced from very early times, but was condemned by early Christian teachers, and ceased almost entirely to be employed among Christian peoples for many centuries. With the elevation of obstetrics once again to a scientific basis by Ambroise Paré and his pupils, artificial interruption of pregnancy for conditions threatening the mother came to be recommended. It was not, however, until the eighteenth century that it came into general use.

The condition above all others which interested the British obstetricians as an indication for the induction of premature labor was a mild degree of pelvic deformity. A meeting of the leading obstetricians was held in London in the year 1756 to discuss the morality of this procedure in cases of contracted pelvis. The operation was approved, and shortly afterward Macauley is credited with performing it for the first time. Doubtless it had been talked about, and probably performed prior to this meeting; nevertheless, it was probably in Great Britain that it was first performed as a definite treatment for pelvic malformation, and for many years it was only in Great Britain that it was practiced as

*Presented at the Tenth Annual Meeting of the Society of Obstetricians and Gynaecologists of Canada, Harrison Hot Springs, B. C., June 11 to 13, 1954.

an accepted obstetrical procedure. In France, owing to the opposition of Baudeloque, the treatment was condemned, and it was not until the year 1831 that it was performed there. In Germany it was accepted earlier, for Wenzel performed it in the year 1809. At the present time it is not favored in any country other than Great Britain as an accepted method of treatment for pelvic disproportion; even in that country it is falling into disrepute and by many it is strongly condemned, especially in the primigravida. It may be of interest to review the various methods which have been employed in the past for bringing about the onset of premature labor. The dates given are those quoted by Fasbender[1] and the following table has been taken from *Operative Obstetrics* by Munro Kerr and Chassar Moir[2]:

1. Medicinal induction (Watson, 1920)
2. Rupture of the membranes (referred to sometimes as the English method, 1756; sometimes as Scheel's method, 1799)
3. Separation of the membranes by forefinger (Hamilton, 1810)
4. Massage of the breasts (Friedrich, 1839)
5. Massage of the uterus (Ulsamer and d'Outrepont, 1820)
6. Sponge tents in the cervix (Brunninghausen, 1820)
7. Injection of fluid under the membranes (Cohen's method, 1846); glycerine (Felzer, 1891); and Aretus paste and similar substances employed in modern times
8. Instrumental dilatation of the cervix, from earliest times
9. Vaginal tampon (Scholler, 1842)
10. Electricity (Herder, 1802), (Shreiber, 1843), (Radford, 1844), (Henning, 1856)
11. Introduction of a catheter. Generally known as Kraus' method (1855), but described by Moir, a pupil of Hamilton some years earlier, and by Mampe in 1838. Soft stomach tube coiled up in the lower pole of the uterus (Fitzgibbon, 1924), Drew Smythe, 1931
12. Hot vaginal douche (Kiwisch, 1846); Scanzoni, hot carbolic douche, 1856
13. Rubber bag in the cervix (Barner, 1861)
14. Metreurynter (Tarnier, 1862, Braun, Muller, Champetier de Ribes, Voorhees). Small rubber balloons (Tarnier, Zweifel, Lowery); animal balloons made from pigs' bladders (Tierblasen)
15. Laminaria tents (Wilson, 1865)
16. Tampon in the cervix (Kehrer, 1888)
17. Paracentesis of the amniotic sac

Most of these methods have now been abandoned and others have been modified, so that today only two methods are largely employed, medical induction, and rupture of the membranes. These methods may be used separately or, as is more popular today, in combination. The introduction of bougies, the insertion of small balloons and metreurynters are not widely used today, although a very interesting article appeared in 1951 on bougie induction of labor by Knerr.[3]

Although the methods for induction of labor have been reduced to two main types, and general agreement appears to exist as to their safety and effectiveness, the indications for induction of labor are still a subject of wide controversy in all countries.

We have seen radical changes of opinion from year to year as to what constitutes an indication for induction of labor, which cases are best treated by allowing them to proceed to term so that labor may come about spontaneously,

and which cases should be treated by elective cesarean section. A diversity of opinion still exists as to the best treatment for the Rh-negative mother who has antibodies. The general practice today is to permit the patient to proceed to term, and carry out replacement transfusions on the infant. In some institutions, however, induction of labor is still being performed before term.

The problem of the postmature infant and its treatment by induction of labor received much criticism and produced many confused thoughts when Calkins[4] published his very interesting paper on this subject. In his series of cases he showed that little increase in the size of the fetus occurred after the two hundred sixtieth day of pregnancy, that labor was not unduly prolonged when the baby was large, and that the amount of ossification which occurred in the fetal skull was negligible.

The treatment of the diabetic mother by induction of labor before the thirty-sixth week of pregnancy has in some institutions been changed, and an effort as been made to allow her to carry the pregnancy to term and permit labor to commence spontaneously. The results of this treatment are not entirely convincing. The original indication for induction of labor, which was cephalopelvic disproportion in the multipara, has in many institutions fallen out of favor.

In spite of the reluctance on the part of some obstetricians to induce labor for a condition which would appear justifiable, a storm of criticism and controversy has been evoked by the present-day practice of elective induction, or, as Erving and Kenwick[5] so aptly named it, "Babies by Appointment." That this procedure is increasing in popularity is undoubtedly true, and that it is practiced by many obstetricians who do not care to admit it openly is also true.

The purpose of this paper is to present my own views on the indications and methods for the induction of labor. The problems of when to induce labor, and how to induce labor do not present real difficulties to the practicing specialists. The teacher of obstetrics, however, may find the subject a thought-provoking one, because upon him rests the responsibility for training the general practitioner-obstetrician, and it is in this group that the misuse and abuse of this procedure are likely to occur with unfavorable results.

It is indeed nearly impossible to teach the intern during his short period on the obstetric service the conditions which should be fulfilled, and the judgment which should be exercised before inducing labor. The elective induction of labor when practiced by the obstetric specialist may even be misleading to the intern, and tend to teach him to treat the whole subject of induction of labor too lightly. He should therefore be taught the methods for inducing labor, the indications for the induction of labor, and these should not include that of elective induction, even though he may perhaps have seen it practiced many times by his teacher. Our maxim therefore should be, "Don't do as I do, but do as I say."

Each patient should be considered individually. A sterile vaginal examination should be carried out to determine the adequacy of the pelvis, the presentation of the fetus, the position of the presenting part, and the state of the cervix.

Should any of these conditions be unfavorable, careful reconsideration is necessary before embarking on induction of labor. The conditions which should be present before labor is induced are that the vertex should be presenting and engaged, the cervix should be ripe, that is, effaced and partially dilated, and there should be no pelvic abnormality.

Indications for Induction of Labor

The indications for induction of labor I would like to consider under three headings: (1) maternal indications, (2) fetal indications, and (3) elective indications.

The following are now considered by me to be justifiable indications for induction of labor:

1. *Maternal Indications.*—
   - A. Toxemias of pregnancy: pre-eclamptic toxemia, mild; pre-eclampsia, severe; eclampsia; hypertensive vascular disease.
   - B. Renal diseases: glomerular nephritis; pyelitis; pyelonephritis.
   - C. Antepartum hemorrhage: placenta previa (marginal and lateral); abruptio placentae.
   - D. Cephalopelvic disproportion?
   - E. Hydramnios: acute, or chronic if associated with fetal abnormality.
2. *Fetal Indications.*—
   - Diabetes mellitus.
   - Postmaturity.
   - Habitual death of the fetus in utero.
3. *Elective Indications.*—
   - Obstetrical and maternal convenience.

Each of these several indications requires some special consideration.

Patients with *toxemia of pregnancy* must be treated by termination of pregnancy if conservative treatment fails to bring the condition under control. It is not desirable to wait for longer than forty-eight hours in the hope that a satisfactory response to treatment may occur, because of the danger of intrauterine death of the fetus. The method selected for termination of pregnancy must be individualized, and either induction of labor carried out if conditions are satisfactory, or a cesarean section performed. If the patient responds satisfactorily to treatment and she is at the thirty-seventh week of pregnancy or later, induction of labor is often the best method of treatment due to the possibility of a flare-up of the toxemia.

Glomerulonephritis may in some cases be treated by induction of labor if the pregnancy has progressed to the thirty-seventh week, or in some instances before the thirty-seventh week when the child is viable, as there is danger of a sudden deterioration in the patient's condition.

Pyelitis and pyelonephritis rarely require termination of pregnancy today because of the effective treatment of the condition with antibiotics. It may still be necessary, however, if a serious infection has been neglected or has failed to respond to treatment, or if blood urea levels begin to rise, indicating serious involvement of the renal parenchyma.

When bleeding associated with *placenta previa* fails to respond to conservative treatment, and examination carried out under suitable circumstances reveals a placenta previa which is situated either laterally or marginally, that is, so long as the placenta is not completely overlapping the internal os, termination of pregnancy is also to be considered. Rupture of the membranes,

with or without the application of Willett scalp traction forceps, is an effective method of treatment. In the case of *abruptio placentae* rupture of the membranes and an intravenous Pitocin drip are effective in some cases.

In the British Isles where *cephalopelvic disproportion* was the original indication for the induction of labor, it is gradually falling into disrepute. In the multipara there may be occasions when induction of labor before term may bring about a successful conclusion to the pregnancy, and so avoid the necessity for a cesarean section.

Acute hydramnios may require termination of pregnancy in order to relieve the distress of the patient. In the chronic form associated with a fetal abnormality which has been confirmed radiologically, induction of labor is indicated.

Diabetes mellitus complicating pregnancy is responsible for a high fetal mortality due to fetal abnormality, hydramnios, toxemia of pregnancy, intrauterine fetal death, and excessively large infants with prolonged labor. Induction of labor prior to the thirty-sixth week of pregnancy still appears to be the treatment of choice, and provides the lowest fetal mortality rate.

Postmaturity is a condition for which induction of labor still remains a subject of controversy. Each case of postmaturity, or alleged postmaturity, must be judged on its own merits. A sterile vaginal examination is the guide to the method of treatment to be adopted. If the head is deeply engaged and the cervix is effaced, induction of labor should be performed. On the other hand, if the head is high and the cervix is long and uneffaced, this patient should not be considered to be at term, regardless of the period of gestation, and an attitude of watchful expectancy should be adopted.

During the latter weeks of pregnancy, without the association of some metabolic disease or hypertension, *habitual death of the fetus* may occur for some still unexplained reason. These cases, if treated by induction of labor prior to term, may often be brought to a successful conclusion by the birth of a living child.

Elective induction of labor for the obstetrician's or the patient's convenience has invoked a great deal of criticism. It has been highly recommended by many eminent obstetricians, and by others of equal eminence it has been severely criticized.

As previously stated, elective induction of labor is being more widely practiced each year, and by many who do not care to admit they are guilty of inducing labor for either their, or the patient's, convenience.

It is my conviction that this practice is good obstetrics, if the conditions for safe induction of labor are fulfilled, and the contraindications fully understood. I have to admit to having practiced this procedure for the past eight years.

The patients whom I have selected for induction of labor have been checked in the office by a sterile vaginal examination, to determine the condition of the cervix, the degree of engagement of the presenting part, and the absence of cephalopelvic disproportion. The contraindications by which I have been guided are: abnormalities of the fetal position or presentation, an unengaged presenting part, pelvic abnormality, a long uneffaced cervix, a dead fetus, and the presence of some maternal contraindication to a vaginal delivery.

The "Baby by Appointment," to borrow a phrase, has many obstetrical advantages. The psychological attitude of the patient is better, because she is properly prepared for parturition. She has only a light breakfast prior to induction of labor, and has been examined prior to the onset of labor to rule out the absence of unfavorable conditions for the conduct of a normal confinement. It has been my experience that such patients generally have a more rapid labor.

The maternal advantages are many. The patient is provided with sufficient time to arrange for suitable help to take over her household responsibilities. If she lives in the country she does not have the worry and anxiety of a hurried trip of 30 to 40 miles or more over country roads, in order to reach the hospital in time for her confinement, or, worse still, she does not have to face the prospect of being snowbound and delivering herself in the farmhouse without help.

Elective induction of labor for these patients, provided the conditions for safe induction are fulfilled, has, in my opinion, decided advantages.

Methods for Induction of Labor

Medical Induction.—

This consists of the giving of 1 to 2 ounces of castor oil, and the administration of an enema in three hours' time. This is followed by the giving of pituitary extract, 2 units at half-hourly intervals for six doses. The more modern method of giving pituitary extract is the use of Pitocin, 0.5 c.c. in 500 c.c. of 5 per cent glucose in water or saline administered intravenously, the infusion being allowed to run at a rate of 10 to 12 drops per minute for a period of 30 minutes, the rate of flow being then gradually increased to 20 to 30 drops per minute until labor is well established.

Operative Induction.—

In present-day obstetrics this consists mainly of amniotomy, and stripping of the membranes around the internal os. The methods of rupturing the membranes are either a simple rupture of the membranes inside the internal os, or rupture of the "hind waters," by the use of a special catheter designed by Drew Smythe.[6]

The use of the Drew Smythe catheter has the following advantages: There is no danger of interference with the presenting part. There is less risk of prolapse of the cord, since intrauterine manipulation is slight, and there is less risk of infection as the catheter may be introduced under direct vision if desirable. The introduction under direct vision can be performed by using a vaginal speculum to expose the cervix; thus when the catheter is being introduced it does not come in contact with the vulva or the vaginal walls.

Combination of Both Methods.—

The combination of amniotomy and a dilute intravenous infusion of Pitocin is, in my opinion, the method of choice for the successful induction of labor. There is rarely a failure and the duration of labor is shortened considerably. Unfavorable complications have apparently occurred, although I have not seen any, nor have I seen any published case reports where unfavorable results have been attributed to the use of intravenous Pitocin. No doubt serious complications will occur with this, as with any method of induction of labor, if care and judgment are not exercised in their use, and if each case is not carefully evaluated.

Summary

Personal views on the indications for and methods of induction of labor have been presented. The conditions which should be fulfilled before labor is induced and the contraindications which I have accepted as my rule and guide for the safe conduct of a case selected for induction of labor have been outlined.

Induction of labor is considered to be a safe and effective method of treatment for various obstetrical and maternal conditions, provided that a degree of skill and judgment is exercised.

A plea has been made to those engaged in the teaching of students, to give instruction in the indications and contraindications. They should instill into them the idea that induction of labor should be treated with respect, as a useful obstetrical procedure, not to be practiced with reckless abandon of the rules governing its use.

Elective induction of labor as a convenience to patient or obstetrician has been discussed, and is considered to be a justifiable procedure, if proper selection of cases for its use is exercised.

The method of choice for induction of labor is considered to be the use of the Drew Smythe intrauterine catheter, together with the administration of Pitocin by the intravenous drip method.

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Medical Arts Clinic.

CULDOSCOPY—AN ADJUNCT IN GYNECOLOGICAL DIAGNOSIS*

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CULDOSCOPY may be defined as the direct visualization of the pelvic viscera by the insertion of a scope into the pouch of Douglas. Albert Decker in 1943 made culdoscopy practical by the simple expedient of placing the patient in the knee-chest rather than in the more usual Trendelenburg position.

Culdoscopy is primarily a diagnostic method. While in the majority of instances pelvic diagnosis can be made on history and bimanual examination alone, there are certain cases where the findings are obscure and where laparotomy is unnecessarily delayed because of inadequate diagnostic methods.

The technique of the procedure is as follows: Since the patient must be able to support herself in the knee-chest position, three anesthetic methods have been used. The first is the local infiltration of 5 c.c. of 1 to 2 per cent Novocain into the posterior fornix. This is preceded by premedication with Demerol or Nembutal. Second, low spinal anesthesia or, third, epidural anesthesia may be used. With the patient in the knee-chest position, a solution of 1:1,000 aqueous Zephiran is applied to the buttocks, perineum, and vulva. The Sims speculum is inserted into the vagina and then 1:1,000 aqueous Zephiran is applied to the walls of the vagina. A single-toothed tenaculum then puts downward traction on the cervix. The trocar and cannula are then inserted through the posterior fornix into the pouch of Douglas. A sudden hiss of air is heard when the trocar is removed. This means that air is rushing into the peritoneal cavity. A source of carbon dioxide may be attached to the cannula and thus eliminate the entrance of atmospheric air.

With the culdoscope in position, one may see the posterior surface of the uterus and the fundus, both tubes, both ovaries with their ovarian ligaments and infundibulopelvic ligaments, the lateral pelvic walls, the posterior surface of the broad ligament, the uterosacral ligaments, the rectum, and sigmoid. With the culdoscope in place, indigo carmine can be injected into the uterus and the dye can be seen dripping out of the fimbriated ends of the tubes, or the site of obstruction can be seen.

The indications for culdoscopy include the following: ectopic pregnancy, infertility, endometriosis, hemorrhagic ovarian cysts with intraperitoneal bleeding and ovarian cysts of undetermined character. The contraindications to culdoscopy are: fixation of tissues in the pouch of Douglas, constitutional disease which makes it impossible for the patient to tolerate the knee-chest position, acute vaginal infections.

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*Presented at the Tenth Annual Meeting of the Society of Obstetricians and Gynaecologists of Canada, Harrison Hot Springs, B. C., June 11 to 13, 1954.

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Culdoscopy is not a dangerous procedure. Perforation of the rectum may occur. This is a *rare* complication. The perforation is extraperitoneal and does not require any intervention. Peritonitis may occur, but this is also rare. Decker and Abarbanel use culdoscopy as an outpatient procedure. Bleeding from the puncture wound may occur. This is usually very slight but may require a suture.

I would now like to review several cases where culdoscopy has been useful.

Ectopic Pregnancy.—

In ectopic pregnancy, where the clinical diagnosis is obvious, as shown by history and pelvic examination, culdoscopy is unnecessary. Instances occur, however, where, even after needle puncture of the pouch of Douglas, examination under anesthesia and diagnostic curettage, the diagnosis of ectopic pregnancy is still in doubt. Further treatment would consist either of watchful waiting or exploratory laparotomy. It is in these cases that the culdoscope may be of inestimable help.

The culdoscopic appearance of recent hemoperitoneum is distinctive. In the knee-chest position, the blood runs out of the pelvis and leaves blood streaks across the pelvic viscera. When bleeding has occurred over several days, clots are formed which become well organized and maintain their pelvic position. Thus a clot may be seen in relation to the broad ligament or on either side of the uterus or at the fundus. The tube can be followed into this blood clot. The ovary can be seen distinct from this blood clot. In a nonruptured case, the distorted tube and corpus luteum can be seen.

Case History.—Mrs. L., aged 39 years, para iii, had her last menstrual period on October 20. Since then she had been spotting variable amounts. Three weeks later a diagnostic curettage was done and a proliferative endometrium was found. The spotting continued.

She was seen in consultation one month later. On pelvic examination, the uterus was slightly enlarged and an irregular, semipultaceous mass was felt in the left fornix area. Culdoscopy was performed. When the peritoneal cavity was entered, streaks of blood were seen on both sides of the posterior surface of the broad ligament and the posterior surface of the uterus. On the fundus one could see a mass of blood clot which involved the upper part of the left ovary, the top of the fundus, and a loop of bowel. The right ovary was normal.

Immediate laparotomy was done. The omentum was found to be adherent to the left tube, to a large blood clot, and a piece of small bowel was adherent to all this. The pathological diagnosis was tubal pregnancy.

Tubal Obstruction.—

In infertility the tubes as a rule can be completely visualized and the extent of adhesions seen. Indigo carmine can be injected into the uterus under pressure and, if the tubes are patent, the dye can be seen dripping out of the fimbriated ends. If tubal obstruction is present, the dye will delineate the exact site of obstruction. If culdoscopy is done in the second half of the menstrual cycle, the corpus luteum may be seen.

Case History.—Mrs. R., aged 27 years, para 0, with a history of tubal inflammation six years previously, complained of infertility of four years' duration. Pelvic examination showed the uterus to be anteverted, anteflexed, 3 inches long, and mobile. The ovaries were normal in size and the tubes could not be felt.

On culdoscopy the left tube could be seen running from the junction of the uterus downward posteriorly and it was thickened, a little tortuous, and had a bulbous end adherent to the posterior surface of the broad ligament. Indigo carmine was injected into the

cervix under pressure. It was seen running into the left tube and distended one-third of the medial end of the tube. The dye also ran into the right tube about half the length, and blue areas of distention could be seen in the tube.

The advantage of this examination was that a positive diagnosis could be given the patient and further needless investigation was avoided.

Eudometriosis.—

In endometriosis, early diagnosis and treatment are especially important in the young woman. In the absence of gross localizing signs, culdoscopy may pick up the early puckering scars, hemorrhagic areas, and chocolate cysts diagnostic of endometriosis.

Case History.—Mrs. M., aged 31 years, gravida ii, para 0, complained of dysmenorrhea and dyspareunia for two years. This patient had two miscarriages, one eleven years and one four years previously. Pelvic examination showed the uterus to be anteverted, anteflexed, 2½ inches long, movable and tender; thickening was felt in the fornices, both ovaries were palpable and exquisitely tender, and the right ovary was normal in size. Some fixation and slight enlargement of the left ovary were felt.

On culdoscopy the right ovary was normal in size and a small follicular cyst and brown stain could be seen on it. The left ovary was adherent to the posterior surface of the broad ligament. Two intensely black patches were seen and two small blebs containing clear fluid were seen on the lower pole.

This patient did not respond to medical treatment. Laparotomy was performed and the culdoscopic findings were confirmed.

Cystic Follicles or Corpora Lutea.—

In follicular or corpus luteum cysts, intraperitoneal bleeding may occur following rupture of the Graafian follicle or of a corpus luteum cyst. This is often associated with irregular bleeding and unilateral pain, and may be confused with an ectopic pregnancy. The culdoscopic view shows the blood clot adherent to the affected ovary and both tubes normal. The treatment of watchful waiting may be pursued with confidence here.

Case History.—Mrs. P., aged 28 years, para i, had her last menstrual period on November 24. She missed the December menses. On January 9 she developed an ache in the left iliac fossa and some spotting. This continued until January 16, when pain was suddenly very severe and was accompanied by symptoms of mild shock and increased external bleeding.

She was seen in consultation that evening and culdoscopy was performed, which showed blood streaks on the posterior surface of the uterus and the broad ligament. A small blood clot was seen on the left ovary between it and the left tube. Adhesions were present between this ovary and tube. The right tube and ovary were normal.

A diagnostic curettage was done and showed an endometrium of follicular character. The patient was treated by observation only and recovered with bed rest. She had a period the following month and had a successful pregnancy immediately following this.

Ovarian Cysts or Carcinoma.—

In evaluating the character of ovarian cysts, culdoscopy was of particular value in the following cases:

Case History.—At the age of 58, Mrs. B. had an annular carcinoma of the splenic flexure removed. No metastases were found at that time. At the age of 60, she developed ascites which was felt to be due to a recurrence of the carcinoma of the bowel. Paracentesis showed malignant cells. About six months after the onset of the ascites, she developed uterine bleeding. She was seen in consultation and because of the difficulty in palpating the abdomen and pelvis, a culdoscopic examination and diagnostic curettage were done.

Culdoscopy showed that the right ovary was cystic and the size of a Japanese orange, the left ovary was the size of a grapefruit and had a white mushy appearance, and the parietal peritoneum was covered with fibrinous exudate.

A diagnosis of carcinoma of the ovary was made. A total hysterectomy and bilateral salpingo-oophorectomy were done several days later. The pathological report was a primary anaplastic serous cystadenocarcinoma of the right ovary with extension to the left ovary.

Case History.—Mrs. N., aged 43 years, was seen in consultation because her doctor had found an asymptomatic ovarian cyst on routine pelvic examination. The examination revealed that the pelvis was normal except that the right ovary was adherent to the side wall of the pelvis and measured 2 to 2½ inches in diameter.

Culdoscopic examination showed that the uterus was normal in size, the omentum was adherent to the fundus, omental strands were adherent to the side wall of the pelvis, the left ovary was normal in size and appearance, the right ovary consisted of a large, simple, thin-walled serous cyst adherent to the side wall of the pelvis. The character of the asymptomatic cyst was explained to the patient. A laparotomy was avoided and the patient continued under observation.

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A CLINICAL PATHOLOGICAL SURVEY OF HYSTERECTOMIES PERFORMED DURING THE PAST TEN YEARS IN A NONTEACHING URBAN HOSPITAL*

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GENERAL hospital staffs in the smaller centers do not dictate policy regarding the performance of standard surgical procedures. The reporting of any given operation or technique is usually the work of the individual concerned. The relatively small number of cases that can be reported usually discourages publication of the work performed in these hospitals. As a result, the great majority of articles dealing with the various procedures emanate from centers where a greater measure of control over the destinies of operations and techniques exists. This fact would be of little interest were it not for the fact that nearly 70 per cent of our population is served by the former group of institutions.

It was for this reason that this paper was prepared. The survey represents a study of the clinical and pathological records of patients in our hospital who have had surgical extirpation of the uterus. The review covers a period of ten years and represents 927 consecutive hysterectomies, of which 160 were vaginal operations.

This ten-year period is an interesting one. It spans an era in which antibiotics were further developed in number and usefulness. Blood transfusion services and recovery rooms became important adjuncts to our operating rooms. Improved anesthesia and anesthetic services and the war experience in early ambulation were extended to our hospitals. To these we may add the doctors who returned to civilian practice after war service and the further addition to our medical communities of men who have advanced their training in the field of gynecology. All these factors are expected to make an impression upon the type of work performed and the results obtained in these past ten years.

TABLE I. HYSTERECTOMIES PERFORMED. JANUARY, 1944, TO DECEMBER, 1953

TYPE OF OPERATION	1953	1952	1951	1950	1949	1948	1947	1946	1945	1944	Total
Abdominal total	50	69	67	63	46	53	27	22	15	11	423
Abdominal subtotal	7	17	18	37	27	30	64	51	47	46	344
Vaginal	16	21	25	28	12	13	12	12	11	10	160
Total											927

In Table I we see a gradual increase in the number of total hysterectomies performed. There is a fairly constant number of vaginal hysterectomies per-

*Presented at the Tenth Annual Meeting of the Society of Obstetricians and Gynaecologists of Canada, Harrison Hot Springs, B. C., June 11 to 13, 1954.

formed each year. Generally speaking, the vaginal procedure was performed upon older patients with genital prolapse or upon patients who were poor surgical risks.

The relative merits of the total and subtotal hysterectomy used to stimulate considerable discussion. In the communities where these operations were not or are not now performed exclusively by surgeons who were trained in pelvic surgery, the procedure selected has usually been the one which the operator could best perform. Men who became surgical "converts" without prior training were often dangerous to the patient and in those localities the two operations were not placed too much upon a competetive basis. Among gynecologists today there is no question as to which is the better procedure. It has taken our smaller centers longer to show a preponderance of total hysterectomies and in our hospital the performance of this operation has risen from 30 per cent in 1944 to 88 per cent in 1953. This trend has been accomplished slowly and with little change in our morbidity and mortality rates, and in the incidence of surgical complications.

Table II shows the age distribution and discloses that the majority of our patients are in the third to the fifth decade of life. Fifty-two per cent of these patients were under 45 years of age. This trend was constant throughout the ten-year period. The age distribution is a little surprising in view of the reputation of this city in regard to its proportion of elderly citizens. It is also a lower age group than that reported by Smith.[1]

TABLE II. AGE DISTRIBUTION

AGE (YEARS)	NUMBER	PER CENT
Under 25	16	1.7
26 to 35	111	11.9
36 to 45	353	38.1
46 to 55	274	29.6
56 to 65	98	10.6
Over 65	75	8.1
	927	100.0

Tables III, IV, and V show data regarding the extent of surgery performed. There is a high incidence of adjunctive removal of the adnexa and in this group an appreciable number of small ovarian follicle cysts, normal corpora lutea, and Fallopian tubes appear in the pathological reports. There were 183 normal appendices removed coincident with abdominal hysterectomy and salpingo-oophorectomy and 36 of these patients were morbid.

TABLE III. THE EXTENT OF SURGERY PERFORMED WITH TOTAL HYSTERECTOMY

Total hysterectomy	71 cases
Total hysterectomy and appendectomy	21
Total hysterectomy and unilateral salpingo-oophorectomy	77
Total hysterectomy, unilateral salpingo-oophorectomy, and appendectomy	39
Total hysterectomy and bilateral salpingo-oophorectomy	164
Total hysterectomy, bilateral salpingo-oophorectomy, and appendectomy	51

While one does not hesitate to remove a diseased appendix at the time that a hysterectomy is performed, it appears that we may be increasing morbidity by casually removing a normal organ as an adjunctive procedure. Our incidence scarcely merits the term "routine" but it is still of sufficient frequency and morbidity to deserve serious thought.

Preliminary dilatation and curettage was performed on 257 occasions, an incidence of about 25 per cent of all cases. If this figure is in error, it is due to the fact that the operator did not make an accurate report. There was a significant number of instances in which the pathologist reported upon curettings from cases in which no reference was made to the curettage in the operative report. The figure just given includes such cases.

TABLE IV. THE EXTENT OF SURGERY PERFORMED WITH SUBTOTAL HYSTERECTOMY

Subtotal hysterectomy	92 cases
Subtotal hysterectomy and appendectomy	40
Subtotal hysterectomy and unilateral salpingo-oophorectomy	39
Subtotal hysterectomy, unilateral salpingo-oophorectomy, and appendectomy	52
Subtotal hysterectomy and bilateral salpingo-oophorectomy	64
Subtotal hysterectomy, bilateral salpingo-oophorectomy, and appendectomy	57

TABLE V. THE EXTENT OF SURGERY PERFORMED WITH VAGINAL HYSTERECTOMY

Vaginal hysterectomy and vaginal plastic repair	127 cases
Vaginal hysterectomy, plastic repair, and adnexal surgery	24
Vaginal hysterectomy, plastic repair, and other adjunctive operations	9

While a preliminary dilatation and curettage may not be a necessary procedure in all cases prior to abdominal hysterectomy, one can hardly credit the performance of a vaginal hysterectomy without this procedure. In the review of vaginal hysterectomies, one endometrial carcinoma was missed in this manner. On the other hand, one other endometrial cancer was missed by the preoperative curettage. There was the unexpected finding of 7 endometrial carcinomas, 3 carcinomas of the cervix, and 4 myosarcomas in uteri removed by abdominal hysterectomy. A preliminary curettage was performed in only 2 of these cases. This has been a serious omission in those instances where the surgery performed was not sufficient to deal adequately with the malignant lesion subsequently found. A subtotal hysterectomy and unilateral salpingo-oophorectomy was the complete treatment for 2 of these cases of endometrial carcinoma. In one other case a total hysterectomy and unilateral salpingo-oophorectomy were performed.

Pathology

The study of the pathological reports and the review of some of the sections have been most instructive. Tables VI and VII are compiled from the pathological reports and while there is some overlapping and duplication, an attempt has been made to list only the significant lesions. Only neoplastic tumors of the ovary are listed and cesarean hysterectomy is excluded.

As one might expect, fibromyomas were the most common lesions reported and were found in 445 cases in which the uterus was removed by abdominal hysterectomy. This is an incidence of 58 per cent and in 186 cases (41 per cent), the largest fibroid reported was less than 5 cm. in diameter. The clinical records of these cases, therefore, were most important in ascertaining the indications for hysterectomy.

There were 394 benign cervical lesions and, of these, 56 constituted the primary pathological lesion reported. Since these lesions of the cervix are found only in those uteri removed by total hysterectomy, they represent an incidence of 93 per cent. Many of them, of course, were very mild conditions.

There were 7 early intrauterine pregnancies. Three were accidental findings and 4 were therapeutic interruptions of the pregnancies for reasons other than the coexistent pelvic lesion.

TABLE VI. PATHOLOGY OF TISSUE REMOVED BY ABDOMINAL HYSTERECTOMY

FINDINGS	NUMBER (CASES)	PER CENT
Fibromyomas	445	58.0
Endometriosis and adenomyosis	105	13.6
Endometrial hyperplasia	73	9.0
Endometrial polyp	54	7.0
Benign cervical disease	394	93.0
Pelvic inflammatory disease	93	12.0
Pelvic tuberculosis	7	0.9
Endometrial carcinoma	47	6.1
Carcinoma of the cervix	4	0.9
Carcinoma in situ of the cervix	2	0.4
Sarcoma of the uterus	5*	0.6
Carcinoma of the ovary	5	0.6
Benign ovarian neoplasms	36	4.6
Extrauterine pregnancy	4	0.5
Intrauterine pregnancy	7	0.9
Retained secundines	2	0.2
Hydatidiform mole	1	---
Rupture or traumatic perforation of uterus	4	0.5
No pathological lesion	96	12.5

*At least one of these cases was a sarcomatous change within a myoma.

TABLE VII. PATHOLOGY OF TISSUE REMOVED BY VAGINAL HYSTERECTOMY

FINDINGS	NO. OF CASES	PER CENT
No pathological lesion	42	26.2
Benign cervical lesion	87	54.3
Fibromyomas	31	19.3
Endometrial hyperplasia	16	10.0
Endometriosis and adenomyosis	5	3.1
Polyps	16	10.0
Endometrial carcinoma	3	1.8
Cancer of the cervix	1	0.6

There was one case of rupture of the gravid uterus through the scar of a previous classical cesarean section. Of the 3 cases of traumatic perforation of the uterus, one patient suffered a postpartum hemorrhage following delivery by classical cesarean section. In the process of evacuating and packing the uterus an instrument was passed through the wound in the fundus and hysterectomy followed. One other case occurred when a uterine polyp was removed by torsion. The posterior wall of the uterus was torn and the serosa perforated. The last case was that of a gravida iii with uterine fibroids who received a medical induction with Pitocin followed by surgical rupture of the membranes. The patient delivered precipitately within ten minutes. In the days following she became febrile, distended, and complained of severe abdominal pain. The surgeon decided to perform a myomectomy. The uterine cavity was opened extensively and hysterectomy followed. This very ill patient recovered.

The incidence of malignant lesions found in tissue removed by abdominal hysterectomy was 8 per cent. In this group were 47 endometrial carcinomas, 40 of which were diagnosed preoperatively. Seven, therefore, were unexpected findings. Added to these there were 2 previously undiagnosed carcinomas of the cervix and 5 sarcomas of the uterus. At least one of these sarcomas occurred as a degenerative change in a myoma. There were 2 carcinomas in situ of the cervix and 5 carcinomas of the ovary.

In 96 cases, no pathological lesion was reported, an incidence of 12.5 per cent. This is only slightly higher than the number of normal uteri reported by Wesley.[2] The majority of our cases occurred prior to 1948 and there has been a striking decline since then, only 4 cases occurring in 1953.

Vaginal hysterectomy is performed in our hospital mainly in the course of treatment for genital prolapse and in the poor-risk patient. The incidence of carcinoma is 2.4 per cent. The one case of cancer of the cervix was a surprise finding. One early endometrial carcinoma was missed by the preliminary curettage. No curettage was performed in the second case. The third case was that of an extremely poor-risk elderly patient in whom the cancer of the body of the uterus had been previously diagnosed and upon whom a vaginal hysterectomy and bilateral salpingo-oophorectomy were performed.

Symptoms

Many pathological lesions were discovered through routine physical examination and the severity of the symptoms recorded is only relative. Generally speaking, however, they follow the classical pattern of gynecological complaints. Vaginal bleeding was the most common single complaint for which patients sought treatment. This group includes profuse and continuous bleeding, intermittent spotting, and abnormalities of menstrual flow.

TABLE VIII. SYMPTOMS (ALL CASES)

COMPLAINT	NO. OF CASES	PER CENT
Vaginal bleeding	486	52.4
Abdominopelvic pain	312	33.6
Prolapse	144	14.4
Urinary symptoms	120	12.9
Low back pain	84	9.0
Secondary symptoms*	68	7.3
Vaginal discharge	65	7.0
Abdominal mass	59	6.3
No symptoms	51	5.5

*Weakness, weight loss, fatigue, insomnia, general malaise, etc.

Morbidity and Mortality

Since there is no standard of morbidity for surgical procedures, the morbidity for this series was determined by the criteria for obstetrics. The lack of a standard of morbidity made it difficult to ascertain the cause in many cases. A considerable number of febrile patients were considered by the surgeon to have no complications and no documentation was made as to the cause of the febrile reaction.

TABLE IX. MORBIDITY

	TOTAL HYSTERECTOMY	SUBTOTAL HYSTERECTOMY	VAGINAL HYSTERECTOMY
Urinary infection	24	13	18
Respiratory infection	12	11	4
Wound infection	27	8	--
Peritonitis	15	10	35
Ileus	12	6	2
Peripheral vascular complications	8	5	1
No indication	21	17	7
Total cases	119	70	67
Per cent	28	20.3	41.8

While our morbidity in abdominal hysterectomy is consistent with that reported in other series, the incidence for vaginal hysterectomy is considerably higher. Pelvic peritonitis or pelvic abscess and urinary infections account for the great majority of these cases.

The cases of ileus are also reported under the surgical complications but these patients were febrile and although the treatment indicated an infectious process, the only recorded cause for morbidity was the ileus. It was thought better to include them under a separate heading than under the "no indication" group.

The peripheral vascular complications were few but when one considers that the majority of our patients were relatively young women in good health, this low incidence is not surprising.

The significance of our morbidity may be reflected in the study of hospital stay and the use of antibiotics. In 1944, 75 per cent of the patients who had an abdominal hysterectomy were in the hospital more than 12 postoperative days. The morbidity in that year was 26 per cent. There was little penicillin available to civilian hospitals in 1944 and few of these patients received chemotherapy. Ten years later, in 1953, only 5.2 per cent of patients upon whom an abdominal hysterectomy was performed remained in the hospital more than 12 days postoperatively. Seventeen and five-tenths per cent were morbid and nearly 70 per cent received antibiotic therapy. In 1944, the morbidity for vaginal hysterectomy was 60 per cent and all these patients remained in the hospital more than 12 days postoperatively. In 1953, 15 of the 16 patients upon whom a vaginal hysterectomy was performed remained in the hospital more than 12 days, 2 patients were morbid, and all but 3 received antibiotic therapy.

The dramatic change in morbidity during this ten-year period occurred in the group of total hysterectomies. The morbidity for this operation was 54.5 per cent in 1944 and had dropped to 20 per cent in 1953. The decline has been steady each year. The morbidity for vaginal hysterectomy has fallen from 60 per cent in 1944 to 12.5 per cent in 1953. The incidence for subtotal hysterectomy has remained relatively unchanged, being 22 per cent in 1944 and 23.5 per cent in 1952. There was no morbidity among the seven cases in 1953.

There were 3 deaths. One occurred following a vaginal hysterectomy which took three hours to perform. The patient developed a strangulated hernia and died of bronchopneumonia following herniotomy. One death occurred following a subtotal hysterectomy performed for advanced carcinoma of the uterus. The patient's condition deteriorated rapidly and she died of carcinomatosis. The third death occurred in 1948. A total hysterectomy and bilateral salpingo-oophorectomy had been performed for endometrial carcinoma. The abdominal wound disrupted on the tenth postoperative day. The bowel was inadvertently perforated during the resuturing of the abdomen, and the patient died of peritonitis.

Surgical Complications

The recognized surgical complications were surprisingly few. Undoubtedly some patients with unrecognized injuries were discharged from the hospital and were perhaps readmitted to another department or to another hospital and therefore are lost to this type of survey.

Two and seven-tenths per cent of our patients had significant postoperative complications. The total incidence of all recognized postoperative complications was 23.6 per cent.

Inadequate preparation of the patient for surgery, improper asepsis, lack of careful handling and approximation of tissue, inattention to hemostasis, and the prolongation of the operation by the performance of unnecessary adjunctive procedures are suggested by the high incidence of incisional hematomas, ileus, and shock. These are thought-provoking figures in spite of the fact that the

majority of our patients were discharged from the hospital within satisfactory limits of postoperative stay. This may further suggest that these complications referred to are more of a nuisance to the patient than a disability. We may be guilty of inattention to minor details, however, and of too much reliance upon the effectiveness of antibiotics and blood replacement.

TABLE X. RECOGNIZED SURGICAL COMPLICATIONS

	TOTAL HYSTERECTOMY	SUBTOTAL HYSTERECTOMY	VAGINAL HYSTERECTOMY
Bladder injury	0	0	1
Injury to ureter	2	0	0
Bowel injury	3	0	1
Wound disruption	5	1	–
Incisional hematoma	31	34	–
Bleeding from vaginal vault	3	3	3
Ileus	36	45	6
Shock	15	11	4
Brachial plexus stretch	3	2	0
Intravascular clotting	3	3	3
Strangulated hernia	0	0	1
Total	101	99	20
Incidence	23.8%	28.7%	11.8%

Comment

One of the big problems of the uterine fibroid is that so many women harbor them. Fibroids constitute the most common indication for hysterectomy. I think that we all agree that the majority of symptomatic fibroids are best treated surgically. Many cases are asymptomatic, however, and we have in this series a group of some 94 patients who were subjected to abdominal hysterectomy who had no symptoms, or their complaints were of such a nature that they could hardly be ascribed to the small tumor found. In following the trend in dealing with this problem these past ten years, we find in our records unmistakable evidence that we are adopting a more conservative attitude with regard to the management of these lesions. The next ten years will see few hysterectomies performed for these small, asymptomatic fibroids.

The findings of this review suggest that we should employ preliminary vaginal examination under anesthesia and dilatation and curettage more often than we apparently do. More attention to the detailed reporting of operative procedures is also indicated.

We are using antibiotics liberally, but their use is probably not the significant factor in the decline in our morbidity. The relatively large numbers of urinary infections, wound infections, incisional hematomas, and ileus suggest that we direct more attention to the preparation of the patient, gentleness in handling tissue, hemostasis, and the performance of unnecessary concomitant procedures. Every center reporting its results has shown improvement in morbidity paralleling improved surgical care and technique. It is well within the capabilities of our smaller hospitals to do likewise.

It is only through the study of information obtained from follow-up examination that we can adequately assess the value and success of our operative procedures. Such studies can assist us in selecting surgical procedure designed

to give our patients the best anatomical and functional results. General hospitals in our smaller cities do not have a system of follow-up study and whereas the surgeon himself may gain satisfaction or not from the results of his individual efforts, they do not become available to his colleagues unless he makes that information available in the records. Much of the value of a survey such as this is lost and only vague conclusions may be reached when the end result of our work is not documented and periodically analyzed.

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CARCINOMA OF THE CERVICAL STUMP*†

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CARCINOMA of the residual cervical stump was first mentioned by Chrobak in 1896. In 1921 Polak collected 256 cases from the literature and since that time there has been an increased interest in the subject.

Young and Jones, reporting on a large series of cases, established an average ratio of 4.1 per cent stump cancer to total cases of carcinoma of the cervix. Some investigators reported a higher incidence than others, for example, Ward found an incidence of 6.7 per cent, Black, an incidence of 8.1 per cent, while Healy and Arneson in a comparable number of cases found an incidence of only 2.6 per cent.

Since attention has been drawn to the proportion of cancer in cervical stumps, there has been considerable discussion in the literature as to the advisability of performing a subtotal hysterectomy as opposed to the total operation. The crux of the matter lies in the determination of whether the mortality of the total operation exceeds the mortality of the subtotal by a number greater or less than the incidence of cancer in the residual cervices.

This has always been difficult to evaluate because of inadequate follow-up of cases where subtotal hysterectomy has been performed and the impossibility of obtaining reliable figures as to the incidence of carcinoma in the cervical stump. Young and Jones in a composite report give the figure 0.45 per cent to 1.0 per cent incidence of malignancy in cervical stumps.

There probably is no doubt that a few decades ago the mortality from total hysterectomy over subtotal hysterectomy was higher than the incidence of cancer in stumps. As recently as 1936, Meigs advised against routine total hysterectomy and advocated the subtotal procedure where complications such as extensive endometriosis, inflammatory disease, etc., existed.

Of late years, with the improvements in surgical training and technique, the discovery of antibiotics and the institution of blood banks, there is no significant difference in the mortality between the two operations and we feel, as do many others, that the total operation is mandatory except in the very occasional case of extensive pelvic inflammatory disease.

Between the years 1926 and 1953, a total of 997 cases of carcinoma of the cervix were seen at the Royal Victoria Montreal Maternity Hospital. Of these, 75 cases, or 7.53 per cent, were carcinomas in residual cervices. This group

*This work was made possible through generous grants from the Cancer Research Society, Inc., Montreal, Quebec.

†Presented at the Tenth Annual Meeting of the Society of Obstetricians and Gynaecologists of Canada, Harrison Hot Springs, B. C., June 11 to 13, 1954.

includes all stumps regardless of the length of time elapsed since supracervical hysterectomy. Actually the time lapse varied from knowledge of the existence of the disease at the time of subtotal hysterectomy to 32 years following the operation (Table I).

TABLE I. INTERVAL BETWEEN SUBTOTAL HYSTERECTOMY AND DIAGNOSIS OF CANCER

0-6 months	11 cases
6 months-2 years	7 cases
2 years-5 years	7 cases
5 years-32 years	50 cases

The age distribution of stump carcinoma in this series showed a peak incidence in the decade 50 to 59 years, as compared with a peak incidence in our non-stump cases in the decade 40 to 49 years (Table II).

TABLE II. AGE DISTRIBUTION

AGE (YEARS)	STUMP CANCER		NON-STUMP CANCER	
	NO. OF CASES	PER CENT	NO. OF CASES	PER CENT
0-29	1	1.33	40	4.3
30-39	9	12	215	23.4
40-49	24	32	286	31.1
50-59	30	40	242	26.2
60+	11	14.67	139	15.0

The clinical staging in this series of stump carcinoma has been converted to the international classification on the basis of an adequate clinical description (Table III).

TABLE III. INTERNATIONAL STAGE

STAGE	STUMP CANCER		NON-STUMP CANCER	
	NO. OF CASES	PER CENT	NO. OF CASES	PER CENT
0	2	2.7	37	3.9
I	33	44.1	338	36.7
II	22	29.3	307	33.4
III	11	14.6	190	20.6
IV	7	9.3	50	5.4

Analysis of these cases from the point of view of parity shows a slightly higher incidence of nulliparity in the stump series than in the non-stump cases. A probable explanation for this is that the pathology which made the hysterectomy necessary, in a number of cases, undoubtedly precluded pregnancy. The incidence of adenocarcinoma of the residual cervix is about the same in both groups (Table IV).

TABLE IV. INCIDENCE OF NULLIPARITY AND OF ADENOCARCINOMA IN CANCER OF THE CERVIX

	STUMP CASES	NON-STUMP CASES
Nulliparas	11, or 14.6%	108, or 11.7%
Adenocarcinoma	4, or 5.3%	40, or 4.3%

The most interesting aspect of this study was the result of treatment in these cases. We have grouped our true stump cancers with the residual cancers for this purpose for we feel that the problem of treatment is similar in these two groups. The striking features of this series can best be brought out

by dividing the entire series into two groups, namely, the cases treated between 1926 and 1938, inclusive, and the cases in the last decade with a five-year follow-up, namely 1939 to 1948, inclusive (Table V).

TABLE V. FIVE-YEAR SURVIVAL RATE

	STUMP CASES	NON-STUMP CASES
1926-1938	6.25%	30.4%
1926-1948	31.4%	35.9%
1939-1948	42.8%	41.8%

There is a striking difference in the five-year survival rate between the first group of stump cases (1926-1938) and the second group (1939-1948). It appears from examination of Table VI that the difference in results may be due partly to the fact that the second group had a higher incidence of early stages of the disease. It also shows, however, that the better results were coincident with larger radium dosage and more frequent use of deep x-ray therapy. It might also be added that the deep x-ray therapy given to the second group had much greater therapeutic value than that given to the first group.

TABLE VI. COMPARISON OF SERIES OF CASES OF CANCER OF THE CERVICAL STUMP TREATED 1926-1938 WITH THOSE TREATED 1939-1948

	GROUP I 1926-1938	GROUP II 1939-1948
Stages 1 and 2	69%	83%
Stages 3 and 4	31%	17%
Average radium dose	2,900 mg. hr.	3,650 mg. hr.
Patients receiving deep x-ray	31%	71%
Five-year survival rate	6.25%	42.8%

We consider vesicovaginal and rectovaginal fistulas as the only definite and readily observable complications of radiation therapy for purposes of comparison between different series. There were 5 cases of fistulas in our 75 cases of stump carcinoma, an incidence of 6.6 per cent which is only slightly higher than in the non-stump series. Of course most of these fistulas are associated with progressing cancer. Actually, there was only one patient out of the 5 who lived over five years. This patient is very interesting in that her rectovaginal fistula healed spontaneously within a year after colostomy and she is now alive and well with her bowels functioning through normal channels.

Conclusions

1. The majority of series of stump carcinoma published to date are relatively small and many of them show some wide variations on a percentage basis as compared with cervix carcinoma when the body of the uterus is present.

2. We feel that analysis of larger series or combining the reported series will cancel out the spurious deviations and make carcinoma of the cervical stump not significantly different in any way except for the method of treatment.

3. A combined incidence of 7 or 8 per cent of stump carcinoma together with the steady decline in mortality and morbidity associated with total hysterectomy makes this operation mandatory today.

4. We agree with Tice that there is little virtue in separating residual stump cancers from true stump cancers. Both present the same problem in treatment, and this treatment should be by means of radiotherapy when the disease is evident clinically. Carcinoma in situ of the cervical stump can of course be treated by surgical extirpation.

5. We feel that carcinoma of the cervical stump should be treated by using the same vault dose of radium as in carcinoma of the cervix when the whole uterus is present, and in addition a canal dose should be administered which is proportional to the length of the residual canal. In this way approximately 60 to 70 per cent of the standard dose can be used in stumps. All cases should have in addition the standard dose of external radiation with few exceptions.

6. Our results show, as did Ward's and Cosbie's, that carcinoma of the cervical stump, when adequately treated, yields results as good as those obtained in the treatment of carcinoma of the cervix when the whole uterus is present.

7. The complications of treatment in our series were not significantly higher than in the non-stump cases.

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THE RETROVERTED UTERUS IN PRIVATE PRACTICE*

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THE material upon which this discussion is based consists of 454 cases of retroversion observed among three thousand consecutive cases in private practice, giving an incidence of 15.1 per cent. Cases requiring Fothergill operations or vaginal hysterectomies were not necessarily considered as cases of retroversion.

Of the 454 cases of retroversion, 48 were subjected to surgery, an operative incidence of 10.5 per cent. In the cases treated nonoperatively, the pessary which was used was almost exclusively of the Hodge type.

Symptoms in Cases of Retroversion

A large number of these cases are symptomless. Of the 454 patients, 260, or 57 per cent, had no symptoms attributable to the retroversion. The most common complaints when any are present are backache, dysmenorrhea, lower abdominal pain, dyspareunia, and bearing down sensations in the pelvis. Symptoms tend to vary with the parity of the patient. For example, dysmenorrhea is most common in the nullipara.

The pathological processes leading to these complaints and due to the retroversion are pelvic congestion, prolapse of one or both ovaries, cystic ovaries, and uterine hypertrophy. Certain conditions are often found, such as endometriosis, pelvic inflammatory disease, and pelvic tumors, which may be due to or caused by retroversion.

Pregnancy and Retroversion

Retroversion is not a frequent cause of sterility but is a factor to be kept in mind. In this series there was one case of closed tubes which was corrected by raising the uterus with a pessary. There were two cases of sterility of long standing, in which retroversion was the only abnormal finding. These two patients became pregnant while wearing a pessary. No uterine suspensions were done for sterility, however.

Eighty-three of the 454 patients became pregnant while under our care, some of them more than once, for a total of 116 pregnancies.

The incidence of spontaneous abortions was 8.5 per cent as compared to 8 per cent in patients with so-called normal anteverted uteri. Impacted uterus

*Presented at the Tenth Annual Meeting of the Society of Obstetricians and Gynaecologists of Canada, Harrison Hot Springs, B. C., June 11 to 13, 1954.

in pregnancy was noted only twice. One, associated with spondylolisthesis, was freed by putting the patient in the knee-chest position and using recto-vaginal manipulation. Laparotomy was necessary in the second and the uterus was raised from this abdominal approach. Neither patient aborted.

Pregnant patients with retroversion do have a much higher incidence of pelvic discomfort, which leads to some apprehension, but the pain, in the vast majority of cases, is relieved by the use of a pessary for the first twelve to sixteen weeks.

Insertion of a pessary when the patient is a habitual aborter and has a retroversion is a routine with us. As this therapy is used with other measures it is almost impossible to evaluate the benefit of the pessary alone.

Postnatal exercises cannot be stressed too strongly. In this series there were 16 cases of retroversion which were corrected in this manner. Five patients acquired retroversion postnatally.

Procedure in the Therapy of Retroversion

If a patient has symptoms attributable to a retroversion uncomplicated by other major pathologic lesions, there are three lines of procedure:

1. If the pelvis is not too tender, a properly fitted pessary is inserted and the patient is instructed to wear this for a month before returning to the office. This has diagnostic as well as therapeutic usefulness. If the uterus is held up and the symptoms are still present, further investigation of the cause of the symptoms is indicated. If the uterus is in normal position and the symptoms are relieved, the pessary is removed and she is asked to return in another month. If, after this, the uterus has fallen back and the symptoms have returned, the pessary is reinserted for two months and the patient given appropriate exercises. Following this, the pessary is again removed for a month and then the case is assessed. If the uterus has fallen back and the symptoms have returned, surgery is indicated.

The effectiveness of this procedure can be judged by the small number of patients, 32, who had uterine suspensions following it. Another valuable point is that if one does resort to surgery after such a therapeutic test, one is practically assured of a good result.

2. A different procedure must be adopted in those patients whose pelves are so tender on examination that to attempt the use of a pessary would be folly. These cases are not common but are very trying to the physician's judgment when they do occur. Antibiotics and heat therapy must be considered first with, when it becomes possible, insertion of a pessary or resort to surgery. In this series the commonest cause of such tenderness was an ovary prolapsed into the cul-de-sac behind the retroverted uterus.

Little or no success in obtaining relief for this group of patients has been obtained by replacing the retroverted uterus under anesthesia.

3. Finally, there is the retroversion which is immovable even under anesthesia. This condition is usually due to adhesions of endometriosis or pelvic inflammatory disease and requires surgery.

Surgical Therapy

In this series there were 48 patients subjected to surgery. Thirty-two of these patients were operated on following relief of symptoms by pessary. These 32 all had modified Gilliam suspensions. Six had posterior vaginal repairs in addition to the suspensions and 10 had plication of the uterosacral ligaments. The appendix was removed in all cases in which it was still present.

Four patients had early endometriosis and were subjected to suspension and presacral neurectomy. One of these cases was interesting in that the patient had aborted six months before and a biopsy from tissue in the cul-de-sac revealed decidual reaction in the aberrant endometrial tissue.

One other case deserves special mention in that the question of therapeutic abortion arose. This girl had extensive endometriosis in the cul-de-sac with the pelvic colon plastered to the lower uterine segment. She was nulliparous and very desirous of a family, so a suspension and presacral neurectomy with freeing of adhesions were carried out. Three months later she became pregnant and shortly had to be hospitalized because of pain. She was carried for a month and abortion was being seriously considered when it came about spontaneously.

Eleven patients, 7 of whom had endometriosis and 4 pelvic inflammatory disease, were subjected to hysterectomy and bilateral salpingo-oophorectomy because of the extensiveness of the disease.

Summary

In a review of 3,000 charts, retroversion was found in 15.1 per cent, of which the majority of cases (57 per cent) were symptomless. Only 25 per cent of the remaining patients had symptoms which required surgery.

Conclusions

Retroversion is a common finding in gynecological practice. In considering it there is no room for the radical view that this condition is always symptomless or the equally radical view that surgery is indicated without the most careful consideration.

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THE LAY USE OF POTASSIUM PERMANGANATE AS AN ABORTIFACIENT*

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IN RECENT years attention has been focused in various parts of North America on the increasing use of potassium permanganate by the public in an attempt, usually futile, to produce abortion. It is apparent from a study of the literature that this practice has been relatively common in Europe and in South America for a considerable period of time, in spite of the fact that the first North American article on the subject appeared in 1941.

In that year Shull[1] presented 17 cases in which potassium permanganate was used as an abortifacient, and dated the first case at the Boston City Hospital in March, 1936. McDonough,[2] in 1945, extended the Boston City Hospital series to 65 cases, and reported that 6 had been successful in producing abortion. He pointed out that in most cases vaginal bleeding took place within two hours of inserting the tablet in the vagina, and in one case which continued to term delivery by section was necessary because of the severe scarring of the cervix from the previously attempted abortion. Jetter and Hunter,[3] in 1949, reported the first fatality from the use of a douche containing a saturated solution of potassium permanganate in which about 7 Gm. of the chemical were dissolved. Carney, in 1953, reviewed the literature and added 20 cases without a fatality or a successful abortion.

Our attention was first directed to this problem by a fatality on our service in November, 1947. Between 1947 and 1953 we have been able to find 10 cases in our hospital, 8 on our own service and 2 from private sources, in which potassium permanganate tablets, either singly or several, had been inserted by the patient in order to produce abortion. In this series there were 2 deaths, 3 abortions, 2 patients continued to term, and 2 were shown not to have been pregnant. In one case the follow-up was lacking and it is not known whether or not the pregnancy continued. The tablets were of 5 grain strength, easily procurable at the drugstore without prescription. The question of sale of this drug over the counter was brought to the attention of the Saint John Medical Society several years ago, and at that time a resolution was passed asking the druggists of the city to refrain from selling potassium permanganate tablets to the public without a prescription.

Summary of Case Reports

Case 1.—No. 7480/47. Mrs. M. H., a 25-year-old gravida vi, para ii, was admitted to our service with a history of low back pains for seven days, and vaginal bleeding for four days. She was five months pregnant, but denied interference. The obstetrical history

*Presented at the Tenth Annual Meeting of the Society of Obstetricians and Gynaecologists of Canada, Harrison Hot Springs, B. C., June 11 to 13, 1954.

included three abortions, one stillbirth at eight months, and one full-term living child delivered in 1947. The present pregnancy had been uneventful until seven days previously.

On admission the patient was in good physical condition, with blood pressure 122/66, temperature 99° F., pulse 112, respirations 20, and hemoglobin estimation 82 per cent, with a red count of 4.6 million. The urine was negative. Pelvic examination was not carried out at that time as the vaginal bleeding was slight. The patient aborted spontaneously four hours after admission. Twelve hours later she began to bleed profusely per vaginam, but responded quickly to antishock therapy, which included blood transfusion. Twenty-four hours after admission she again went into shock, and died despite emergency measures. The total urinary output during her stay in hospital was 2 ounces, obtained shortly after admission. Unfortunately it was not possible to obtain permission for postmortem.

We present this case as our first chemical burn to the vagina, since follow-up questioning of the family established that potassium permanganate was used to effect an abortion. We are of the opinion that a blood vessel in the genital tract eroded shortly after admission, producing the initial episode of shock from rapid blood loss. In response to antishock therapy her blood pressure was restored and her general condition was then considered to be satisfactory. The terminal episode of shock was the result of further blood loss to the point of exsanguination.

CASE 2.—No. 13425/48. Mrs. R. M., a 25-year-old white woman, was admitted to the hospital with a history of vaginal bleeding for an undetermined period of time. The general physical condition of the patient was good, with temperature 98° F., pulse 56, respirations 20, and a hemoglobin estimation of 79 per cent. The Xenopus pregnancy test was positive. Pelvic examination revealed the presence of a chemical burn to the cervix. Treatment consisted of warm saline douches and topical and systemic penicillin therapy. Questioning elicited the information that potassium permanganate had been inserted into the vagina to effect abortion. The patient was discharged from the hospital on the fourteenth day, with the cervical lesion healing well and the pregnancy progressing normally.

It is not known how long prior to the bleeding the tablet was inserted.

CASE 3.—No. 32511/50. Mrs. J. G., a 27-year-old white woman, was admitted to the hospital with a history of bleeding per vaginam for four hours. The products of conception were believed to have been passed prior to admission. No information was available as to the length of the gestational period.

General physical examination revealed a very pale young adult, with a blood pressure of 120/70, temperature 97° F., pulse 120, respirations 22, and a hemoglobin estimation of 46 per cent. Immediate treatment included 1,000 c.c. of whole blood. On the following day an examination under anesthesia showed the uterus to be the size of an eight weeks' pregnancy. The cervix was closed. Four ulcers were noted on the posterior vaginal wall. There was active bleeding from one ulcer, and a suture was required to control this bleeding. A dilatation and curettage revealed no tissue within the uterus. The uterus and vagina were tightly packed for forty-eight hours. The patient was discharged on the ninth day with all burned areas clean and healing.

CASE 4.—No. 27051/50. Miss P. C., a 20-year-old white woman, was admitted to the hospital with a history of vaginal bleeding for twenty-four hours. She claimed to be three months pregnant.

General physical examination revealed the patient to be in severe shock, with the blood pressure 60/0, temperature 96.6° F., pulse 120, and respirations 22. Immediate treatment included 500 c.c. of whole blood, to which the patient responded satisfactorily.

Nineteen hours after admission the patient was found lying on the bathroom floor in a pool of blood in an unconscious state. She died very soon after, despite emergency measures.

At autopsy there was marked generalized pallor and all organs were practically bloodless. The lungs showed atelectasis. The kidneys showed "swelling of the tubular epithelium and small granules of bile-like pigment in the cytoplasm of the cells lining the collecting tubules." Inspection of the vagina showed "four separate areas of ulceration,

each about 2 cm. in diameter. These ulcers had a punched-out appearance and their bases were very red. In the base of one ulcer, on the postero-lateral vaginal wall, about five cm. from the cervix, there was a medium sized artery with a large section of its wall missing. Fluid blood flowed freely from this vessel.'' The uterus ''contained a perfectly formed female fetus of about six months' gestation.'' All other systems were negative.

The pathological findings are in keeping with the history of profuse bleeding and severe shock as the result of erosion of an artery in the genital tract. It is apparent in retrospect that the initial shock should have been treated with more than 500 c.c. of blood, and that the patient should have been watched more closely for hemorrhage.

CASE 5.—No. 39765/51. Miss M. R., a 27-year-old white woman, was admitted to the hospital with a history of vaginal bleeding for three hours. She stated that she had inserted two 5-grain tablets of potassium permanganate into the vagina three days ago, when her expected menstrual period did not materialize. Vaginal bleeding began fifty hours after the tablets were inserted.

General physical examination was negative. Pelvic examination revealed the presence of three large, irregular, dark, superficial ulcers, extending around the circumference of the proximal third of the vagina. The uterus and cervix were normal, and it was felt that she had had an abortion. Treatment consisted of low pressure douches twice daily, and systemic penicillin. She was discharged on the sixth day with the ulcers healing well.

The patient was readmitted five days later because of bleeding from one of the ulcers in the vagina. Lochia was noted coming from the cervix, confirming our impression of an abortion at the time of her first admission. She was treated by vaginal packing, which controlled the bleeding, and discharged on the twelfth day with all ulcers healed.

This case points out the danger of late bleeding from these ulcers, which like all burns are rather slow in healing. We feel that patients should be kept in the hospital a sufficient length of time to ensure adequate healing of the lesion, or, failing that, to be cautioned to report back at the first sign of excessive bleeding.

CASE 6.—No. 35079/51. Mrs. E. F., a 24-year-old white woman, was admitted with a diagnosis of incomplete abortion. She was pale on admission, with a rapid pulse and moderately severe vaginal bleeding. Pelvic examination revealed a small ulcer in the left vaginal vault, which was bleeding moderately. The vagina was packed, she was given 1,000 c.c. of whole blood, and made an uneventful recovery, being discharged on the sixteenth day. The patient admitted inserting a potassium permanganate tablet in the vagina. The pregnancy test was negative on discharge. It was felt doubtful whether this patient was pregnant.

CASE 7.—No. 2284/52. Mrs. B. G., an 18-year-old gravida i, para i, was admitted to the hospital by ambulance with a history of severe vaginal bleeding for eight hours. She gave a history of having gone eighteen days past her expected menses. Pelvic examination revealed copious bleeding, and a large eroded area on the right wall of the vagina near the cervix, with a smaller ulcer on the left. The uterus was curetted with the removal of a small amount of tissue, which on section was normal endometrium. The vagina was packed with Oxycel and dry gauze. Forty-eight hours later the patient bled through the packing, which was removed and the vagina repacked. She was given 500 c.c. of whole blood and discharged after ten days in the hospital. On questioning, the patient admitted inserting a potassium permanganate tablet in the vagina.

CASE 8.—No. 7647/53. Mrs. A. C., a 33-year-old gravida v, para iv, was admitted to the hospital with complaints of vaginal bleeding. Shortly after admission she went into shock and was given 1,000 c.c. of whole blood. Examination revealed a large shallow ulcer with a dark necrotic base, about the size of a twenty-five-cent piece. This began on the anterior lip of the cervix and extended into the anterior fornix. Arterial bleeding was present in this area. Under anesthesia the necrotic tissue was removed and the deep

fascia approximated with sutures. The patient stated she had inserted potassium permanganate tablets in the vagina after going two weeks past her period. The first tablet was inserted at that time, and when no result was obtained a second tablet was inserted a week later. The following day she began to bleed and was admitted. She was discharged on the ninth day. We have no evidence that she was pregnant.

Since this patient inserted two tablets a week apart before producing any bleeding it is more than likely that the first tablet did not remain in the vagina very long.

CASE 9.—No. 15449/53. A 26-year-old gravida v, para iv, was admitted to the hospital five months pregnant, with a history of irregular vaginal bleeding. She admitted inserting potassium permanganate tablets some three months previously, and had bled intermittently until admission. The patient was found to have an ulcer 2 cm. in diameter occupying the left lateral wall of the vagina at the level of the cervix. The vagina was packed, but this did not control the bleeding and it was necessary to suture the area. The hemoglobin was 7.8 Gm. on admission and the patient was given 1,000 c.c. of blood during her stay in hospital. She was discharged on the ninth day with the pregnancy continuing normally.

CASE 10.—No. 15552/53. This patient was a 23-year-old white woman who was admitted to the hospital with a diagnosis of incomplete abortion. Vaginal bleeding was not heavy. Pelvic examination revealed an ulcer 2 by 3 cm. in the posterior vaginal vault, superficial in nature. The cervical canal was slightly open and the uterus was curetted. Microscopic examination revealed decidual remnants. The patient signed herself out on the sixth day. There was no admission of using potassium permanganate in this case, but the findings were so typical that the case is included here.

Comment

Jetter and Hunter, in an exhaustive study on the effects of potassium permanganate both locally and systemically, point out that the action of the substance on the vaginal mucosa can be explained by the following formula:

$$4\ KMnO_4 + 2\ H_2O \rightarrow 4\ KOH + 2\ Mn_2O_7$$
$$2\ Mn_2O_7 \rightarrow 4\ MnO_2 + 3\ O_2$$

Potassium permanganate is a strong oxidizing agent, reacting promptly with the protoplasm to produce necrosis, and at the same time undergoing reduction to the brown, almost completely insoluble, oxides of manganese. This brown staining of the tissues is pathognomonic of the potassium permanganate reaction. The prompt interreaction of the chemical and the tissue results in the superficial necrosis noted initially, with the later effect due to the caustic potassium hydroxide penetrating into the deeper tissues.

There is evidence also that potassium permanganate acts as a systemic poison. When ingested in doses of 10 to 20 Gm., which is considered lethal, it acts as an acute hemolytic agent, and has been shown to cause lower nephron nephrosis. It has also been suggested that late collapse and death may be due to hyperpotassemia. The manganese dioxide, though almost insoluble, will cause convulsions and coma in animals. In the case quoted by Jetter and Hunter in which the patient died after using a saturated solution of the chemical as a vaginal douche, autopsy revealed typical mahogany brown staining of the uterine musculature, and to a lesser extent of the other organs as well. The renal tubules contained brown casts.

We may say, therefore, that death from potassium permanganate may be due to one or more of three causes: (1) circulatory collapse due to the local

injury and resultant blood loss; (2) intravascular hemolysis; (3) hyperpotassemia, which is considered more likely to be caused by liberation of intracellular potassium by the hemolytic action of the chemical than by the absorption of potassium from the chemical itself. It is obvious that the damage by potassium permanganate will depend on the amount of the chemical used, the concentration, the length of time that it is permitted to act, and the site of injury. When used locally the initial necrotizing effect is usually attended by severe pain, and the patient as a rule seeks medical aid quickly. By the same token the diagnosis can easily be missed, as the patient presents herself with vaginal bleeding, abdominal pain, and a history of having missed one or more periods. If shock is present, one is even more likely to treat the case as an incomplete abortion, although in so doing the lesion in the vaginal tract will usually be found and the true nature of the condition will then appear.

Questioning revealed that in 3 of the nonfatal cases the tablets were placed in absorbent cotton and inserted into the vagina. By this method the interaction of the vaginal secretions and the chemical was delayed by the absorbent cotton, and the concentration of potassium permanganate in contact with the mucosa was much decreased from what would be expected had the pills been placed in direct contact with the mucosa. In each case the patient stated that the onset of severe pain necessitated the removal of the absorbent cotton plug. We have no information on the method of insertion in the 2 fatal cases, nor in the other 5 cases in which the patient recovered.

Diagnosis

Careful attention to the history in these cases will reveal that the pain, unlike the intermittent crampy pains of abortion, is steady in character, and is located immediately over the suprapubic area. In addition to this, the bleeding is usually more severe than would be expected of an abortion in the early stage in which most of these patients are seen; and the amount of shock is sometimes disproportionate to the amount of blood loss, although it is recognized that this latter is difficult of assessment.

Digital examination will occasionally indicate the presence of deep ulcers. The finding of dark granules of manganese dioxide or the presence of bits of the tablet are pathognomonic. Careful speculum examination will always make the diagnosis clear, provided that care is taken to visualize all parts of the vaginal vault. The burns are generally found on the posterior fornix, the posterior surface of the cervix, and the posterior wall of the vagina.

Treatment

There is little to be said in this regard. The superficial ulcers may require no treatment, or at the most firm packing for forty-eight hours. It is felt advisable to use low pressure douches to remove the excess chemical from the vagina in an effort to negate the later penetration of the tissues by potassium hydroxide. The deep ulcers will require suturing; otherwise, firm packing of the vagina for forty-eight to ninety-six hours is indicated. We have

used systemic penicillin to reduce the possibility of secondary infection of the ulcers. As previously mentioned, these patients should be observed for a longer period of time than the patient with uncomplicated abortion, due to the danger of secondary hemorrhage from the ulcers.

A small amount of distortion and heaping up of the vaginal mucosa can be seen at the site of the ulceration following complete healing. We have not seen any severe distortion of the vaginal walls or cervix as reported by McDonough.[2]

A fatal outcome may result from erosion of a blood vessel and severe blood loss, as demonstrated in our two fatal cases.

Summary

1. Ten cases of chemical burns to the vagina from the use of potassium permanganate as an abortifacient have been presented.

2. Four patients were successful in producing an abortion, two were not pregnant at all, and the rest carried on with their pregnancies.

3. Two deaths in our series of 10 cases are reported. Both of these should have been prevented.

4. We believe that the findings of continuous, severe suprapubic pain, associated with bright red bleeding from the vagina, and particularly if the bleeding is intermittent and associated with shock, should lead to the suspicion of a chemical burn to the vagina.

5. We believe that the medical profession should be made conscious of the increasing frequency of this method of attempted abortion, and that the unrestricted sale of potassium permanganate should be curtailed, as this chemical can no longer be considered a necessary part of our present-day therapeutic armamentarium.

Addendum.—Since presentation of this paper, I have had two more private cases of chemical burn by this drug. Both of these patients recovered uneventfully after primary suture of the ulcers. In both cases pregnancy is continuing.

I wish to express my thanks to two of my friends for permission to include two of their private cases in this study; and my appreciation to Dr. M. B. Wall, a former Resident on our service, for his help in sorting out the case reports.

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POLIOMYELITIS IN PREGNANCY*

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POLIOMYELITIS, once mainly restricted to infants and children, is now a disease to which no age group is immune. Indeed, there is evidence that a greater proportion of severe cases occur in the adult age group. With this changing age incidence there is an increasing number of pregnant women contracting poliomyelitis, making this combination a relatively common clinical problem.

A review of the literature suggests that pregnancy complicating poliomyelitis was a rarity up until about ten years ago. McGoogan[1] reported that the first published case was in 1906. By 1941 Aycock[2] collected 28 cases from the literature and reported an additional 28. Weaver and Steiner[3] listed 75 cases collected up to 1944. By 1953 Bowers and Danforth[4] were able to find 586 cases in the literature and added 24 new cases.

It is the purpose of this paper to record our experiences during a large epidemic and to discuss the incidence of poliomyelitis in pregnancy as well as the effects of one condition on the other.

Case Material

This report deals with 51 cases admitted to the acute poliomyelitis service of the Winnipeg Municipal Hospitals during the five months from July to November, 1953. During this time a total of 1,158 cases were admitted here and 2,284 cases were reported in Manitoba. The severity of the epidemic is indicated by the incidence of 338 reported cases in 1953 per 100,000 population of Greater Winnipeg. As far as can be determined, this figure has only once been exceeded in cities of comparable size; in 1916 in Newark, N. J., there were 340 cases per 100,000 population.[5]

In all cases the diagnosis was confirmed by the appearance of typical paralysis or typical changes in the spinal fluid, or both. Although it was hospital policy not to admit cases without paralysis, there were exceptions to this. All pregnant women except two who presented for admission were admitted. Therefore, the proportion of nonparalytic cases was higher in the pregnant group than in the nonpregnant.

The 51 cases admitted are summarized in Table I.

The Effects of Pregnancy on Poliomyelitis

Susceptibility of Pregnant Women to Poliomyelitis.—

Fig. 1 shows a breakdown of all admissions with particular reference to the pregnant women. It is seen that the male admissions predominate over

*Presented at the Tenth Annual Meeting of the Society of Obstetricians and Gynaecologists of Canada, Harrison Hot Springs, B. C., June 11 to 13, 1954.

TABLE I. SUMMARY OF FIFTY-ONE CASES AT THE WINNIPEG MUNICIPAL HOSPITALS

CASE NO.	AGE	GRA-VIDITY	ON ADMISSION				DELIVERY			MATERNAL RESULT	
			DAYS OF ILLNESS	MONTHS OF PREG-NANCY	CEREBRO-SPINAL FLUID CELL COUNT	PARALYSIS	DAYS FROM ONSET OF POLIO	METHOD	FETAL RESULT	HOS-PITAL DAYS	RESULT
1	28	v	10	5½	368	None	131	?	Normal male 7 pounds, 7 ounces	20	Recovered
2	22	i	5	2	325	Bulbospinal Respirator	(6)	Spontaneous	Abortion	106	Moderate residual paralysis
3	30	iii	5	2	–	Low spinal	215	Spontaneous Vertex	Normal male 8 pounds	94	Moderate residual paralysis
4	36	iv	6	3	70	None	184	Spontaneous Vertex	Normal	13	Recovered
5	35	iii	4	5	144	Spinal	141	Spontaneous Vertex	Normal female 8 pounds	241	Severe residual paralysis
6	20	ii	6	3	90	None	162	Spontaneous Vertex	Normal	8	Recovered
7	19	i	2	4	0	Low spinal	?	?	?	8	?
8*	21	iii	4	4½	1,080	Low spinal	166	Spontaneous Vertex	Female 4 pounds, 14 ounces Clubfeet	261	Severe residual paralysis
9	28	iv	5	2½	45	Spinal	(22)	Spontaneous	Abortion	206	Moderate residual paralysis
10*	25	ii	3	Term	–	Bulbospinal Tracheotomy Respirator	7	Low forceps Vertex	Normal male 7 pounds, 5 ounces	Still in	Requires respirator and tracheotomy
11	26	ii	2	5	255	Low spinal	114	Spontaneous Vertex	Normal male	13	Slight residual paralysis
12*	19	i	4	Term	77	Bulbospinal	6	Low forceps Vertex	Normal male	102	Moderate residual paralysis
13	26	?	6	2	–	Bulbospinal Tracheotomy Respirator	(28)	Spontaneous	Abortion	99	Died of secondary infection

14	22	iii	6	5	144	Bulbar	128	Spontaneous Vertex	Normal male 6 pounds, 8 ounces	11	Recovered
15	36	iv	2	6	560	None	57	Spontaneous Vertex	Premature 3 pounds, 3 ounces Died 4 hours post-partum	8	Recovered
16	24	ii	5	3	370	Spinal	(9)	Spontaneous	Abortion	238	Severe residual paralysis
17*	24	ii	6	Term	205	Bulbospinal Tracheotomy Respirator	9	Spontaneous Vertex	Normal female	17	Died of gastrointestinal hemorrhage
18	19	ii	6	5	230	None	136	Spontaneous Vertex	Normal	10	Recovered
19*	24	ii	4	Term	–	Spinal	15	Low forceps Vertex	Stillbirth	271	Moderate residual paralysis
20	24	iv	2	6	150	None	117	Spontaneous Vertex	Normal	10	Recovered
21	25	ii	7	2	155	Low spinal	(13)	Spontaneous	Abortion	64	Moderate residual paralysis
22	26	ii	1	8	130	Spinal	15	Cesarean	Normal female 7 pounds, 6 ounces	9	Slight residual paralysis plus pre-existing traumatic paraplegia
23	29	iii	5	3½	35	High spinal	184	Spontaneous Vertex	Normal male 6 pounds, 6 ounces	11	Moderate residual paralysis
24	20	i	6	2	20	Low spinal	262	Low forceps Vertex	Normal	15	Slight residual paralysis
25	28	ii	8	3½	450	Bulbospinal Tracheotomy Respirator	(7)	Spontaneous	Abortion	18	Died of perforated duodenal ulcer
26	25	iv	7	8	20	Low spinal	31	Spontaneous Vertex	Congenital heart disease Died few hours postpartum	13	Recovered

TABLE I—CONT'D

CASE NO.	AGE	GRAVIDITY	ON ADMISSION				DELIVERY			MATERNAL RESULT	
			DAYS OF ILLNESS	MONTHS OF PREGNANCY	CEREBROSPINAL FLUID CELL COUNT	PARALYSIS	DAYS FROM ONSET OF POLIO	METHOD	FETAL RESULT	HOSPITAL DAYS	RESULT
27*	29	ii	3	4	55	Low spinal	157	Transverse lie. Internal version, breech extraction	Normal female 7 pounds, 1 ounce	232	Severe residual paralysis
28	19	ii	79	PP	–	Spinal	25	Spontaneous Vertex	Normal female 8 pounds, 10 ounces	Still in	Severe residual paralysis
29	24	ii	8	8½	–	Spinal	66	Spontaneous Vertex	Normal male 7 pounds, 5 ounces	29	Moderate residual paralysis
30	23	ii	10	8	–	Spinal	50	Spontaneous Vertex	Normal	38	Slight residual paralysis
31	22	ii	9	Term	130	Bulbospinal Tracheotomy Respirator	–	–	Undelivered	11	Died of gastrointestinal hemorrhage
32	30	ii	3	8½	–	Bulbospinal Tracheotomy Respirator	–	–	Undelivered	5	Died of gastrointestinal hemorrhage
33*	31	iii	5	7	464	Bulbospinal Tracheotomy Respirator	10	Spontaneous Vertex	Female 2 pounds, 8 ounces. Died seventh day. Bilateral subarachnoid hemorrhage	5	Died with atelectasis and bronchopneumonia
34	28	iii	5	6	375	Low spinal	101	Low forceps Vertex	Normal male	27	Slight residual paralysis
35	25	iii	3	2	850	Low spinal	190	?	Normal male 5 pounds, 13 ounces	12	Recovered
36*	22	i	9	6	645	Spinal Respirator	60	Forceps Breech	Normal female 5 pounds, 12 ounces	Still in	Requires respirator

37*	29	ii	4	8½	88	Spinal	23	Low forceps Vertex	Normal male	254	Severe residual paralysis
38*	27	iii	5	4½	17	Low spinal	151	Low forceps Vertex	Normal male 4 pounds	26	Slight residual paralysis
39	24	iii	2	4½	380	Spinal	160	Spontaneous Vertex	Normal female 7 pounds, 5 ounces	8	Recovered
40	35	ii	3	8	212	None	26	Spontaneous Vertex	Normal	10	Recovered
41*	22	i	5	3	290	Spinal	166	Low forceps Vertex	6 weeks premature female 3 pounds, 3 ounces	229	Toxemia with hypertension—recovered. Slight residual paralysis
42	25	ii	3	5	730	Low spinal	113	Spontaneous Vertex	Normal male 8 pounds, 12 ounces	35	Slight residual paralysis
43*	25	ii	6	8	213	Bulbospinal Respirator	11	Low forceps Vertex	Normal male 5 pounds, 9 ounces	Still in	Severe residual paralysis
44	32	iii	4	3	93	Low spinal	149	Spontaneous Vertex	Five weeks premature	14	Slight residual paralysis
45*	30	iv	3	9	–	Low spinal	8	Low forceps Vertex	Normal	154	Severe residual paralysis
46	23	?	4	6	240	None	137	Spontaneous Vertex	Normal female 6 pounds, 14 ounces	8	Recovered
47	28	iv	1	4	600	None	137	Spontaneous Vertex	Normal male	5	Recovered
48	24	v	4	PP	316	None	4	Spontaneous Vertex	Male 6 pounds, 3 ounces Died eighth day	12	Recovered
49	25	ii	1	3	120	None	(82)	Spontaneous	Abortion	9	Recovered
50	16	i	5	4	83	None	188	Spontaneous Vertex	Normal female 6 pounds, 14 ounces	18	Recovered
51	38	xi	6	3	130	Spinal			Not yet delivered†	98	Moderate residual paralysis

*Patients delivered by one of us (W. J. McC.).
†Since the time of writing, Case 51 has been delivered of a normal 8 pound female infant. We have failed to contact Case 7.

the females in a ratio 1.3 to 1. The occurrence of 51 pregnancies among the 153 married women in the reproductive age group (15 to 44 years) seems to indicate either a remarkably high incidence of pregnancy in the population, the selective admission of pregnant women, or an increased susceptibility of pregnant women to poliomyelitis.

Reports in the literature on the susceptibility of pregnant women to poliomyelitis vary. Aycock[6] and Priddle, Lenz, Young, and Stevenson[7] report an increased incidence of poliomyelitis in pregnancy. This was also found by Weinstein, Aycock, and Feemster,[8] who did not consider the increased incidence due to selective admission of pregnant women to the hospital. Bowers and Danforth[4] in 1953 maintained that there were no convincing data to support the claim that pregnancy increases susceptibility to poliomyelitis but they did not analyze their own data in this respect. This criticism is possibly valid because the other authors[6, 7, 8] compared the number of admissions of pregnant women during an epidemic period to the estimated number of women pregnant in the population at any given time. By failing to allow for the turnover in the pregnant population during the epidemic they underestimated the number at risk and so weighted the evidence in favor of their conclusions.

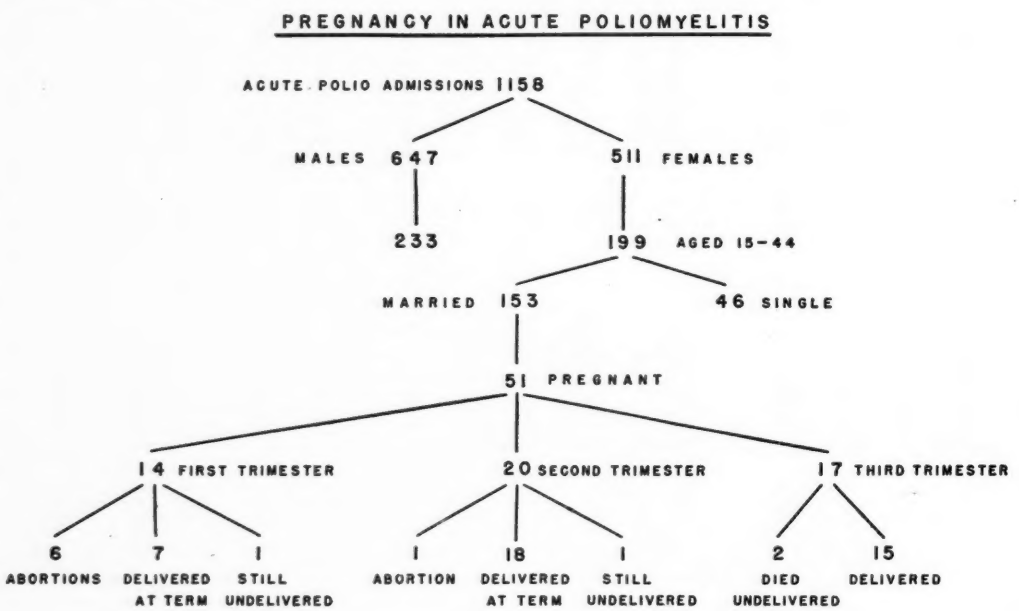

Fig. 1.

In the current series the number of pregnant women admitted has been considered month by month during the five months of the epidemic (Table II). The admission rate per month was compared to the calculated number of pregnant women in the population during the respective months. This is shown in Fig. 2 where the incidence of admissions of pregnant women is compared with the incidence of admissions of married nonpregnant women, single women, and men, all in the same 15 to 44 year age group. The four groups were compared for each of the five months by applying the method of the standard error of the difference between two proportions.[9] Probability values were derived from Student's table of "t." Although the incidence of admissions for pregnant women is significantly greater than for the other groups during August and September ($P < .05$ in each case), this finding should be considered in the

light of our method for estimating the populations of the various groups. The influence of selective admissions must also be considered.

The total numbers of men, married women, and single women in the age group under consideration were obtained from the 1951 census (168,190, 113,700, and 57,000, respectively). The population of pregnant women was calculated from the monthly record of live births in Manitoba for 1953. As there was little fluctuation in the birth rate from month to month, nine-twelfths of the total live births for the year (21,500) plus an additional 10 per cent to allow for fetal wastage was thought to represent a close approximation to the number of pregnant women in the population during any one month (17,700). This does not take into account the number of new pregnancies occurring in any one month. It should be noted, however, that no admissions during the first month of pregnancy were recognized as such. These two sources of error tend to cancel each other. The married nonpregnant group was derived by subtracting the number of pregnancies at any one time from the total number of married women in the appropriate age group.

TABLE II. ADMISSIONS BY MONTHS, AGES 15 TO 44

		JULY	AUG.	SEPT.	OCT.	NOV.	TOTAL
Females.—							
Pregnant:	Total	7	21	16	5	2	51
	Paralytic	4	18	15	1	1	39
Married nonpregnant:							
	Total	15	38	37	7	5	102
	Paralytic	11	35	31	6	4	87
Single:	Total	3	28	10	3	2	46
	Paralytic	3	25	8	1	1	38
Males.—							
	Total	47	98	52	25	11	233
	Paralytic	39	82	47	20	10	198

A possible fallacy in these calculations was the selective admission of nonparalytic pregnant patients mentioned earlier. As there was no discrimination against the admission of any patient with paralysis a comparison of the cases of paralysis should rule out any bias in favor of the cases of pregnancy. This was done by the same method (standard error of the difference between two proportions) and again the proportion of admissions of pregnant women was significantly higher than those of the other groups for August and September ($P < .05$ and $< .02$, respectively).

The P values noted in each case apply to the comparison of the pregnant group with whichever of the other three groups that had the highest admission rate for that month. For August the comparison is with the adult males and for September with the married nonpregnant females.

We conclude from this analysis that pregnant women probably have a greater susceptibility to poliomyelitis.

It can be seen from Fig. 1 that there is a relatively even distribution of cases between three trimesters, suggesting that pregnant women are equally susceptible throughout the course of pregnancy. It has already been noted that no cases were detected in the first month of pregnancy.

Maternal Mortality and Morbidity.—

If pregnancy predisposes to poliomyelitis one might expect the disease to be more severe in this group. Table III shows a comparison of the pregnant patients with the three other groups of adult patients in the same age range admitted during the same five-month epidemic period. It can be seen that the fatality rate was much the same for all these groups.

TABLE III. COMPARISON OF PREGNANT WOMEN WITH OTHER ADULT GROUPS

GROUPS AGED 15-44 YEARS	TOTAL	PARALYZED	RESPIRATOR	TRACHEOTOMY	DEATHS
Females:					
Pregnant	51	39	10	7	6
Single	46	38	5	5	6
Married nonpregnant	102	87	29	15	13
Males	233	198	70	48	28

The mortality rate in the third trimester of pregnancy has been reported to be high.[4, 11] Table IV shows the pregnancy cases by trimesters. Although there were more deaths in the third trimester, we consider the numbers of cases to be too small to draw any conclusions, particularly as the whole pregnant group had a mortality similar to that of other adults in the same age range. Table V lists the causes of maternal death. Autopsies were carried out on 4 of the 6 patients that died. It will be noted that death was caused by complications of the poliomyelitis rather than by the pregnancy. Case 13 died of intercurrent infection three months after onset. She had aborted during the acute phase but was left with widespread paralysis requiring constant respirator care.

TABLE IV. PREGNANT WOMEN BY TRIMESTERS

TRIMESTER	TOTAL	PARALYZED	RESPIRATOR	TRACHEOTOMY	DEATHS
First	14	11	2	1	1
Second	20	13	2	1	1
Third	17	15	6	5	4
Total	51	39	10	7	6

TABLE V. MATERNAL DEATHS

CASE NO.	DAYS IN HOSPITAL	CAUSE OF DEATH	RESULT OF PREGNANCY
13	100	Bronchopneumonia Pyopneumothorax	Abortion
17	11	Gastrointestinal hemorrhage	Live baby at term
25*	10	Perforated duodenal erosion	Abortion
31*	2	Gastrointestinal hemorrhage	Died undelivered
32*	2	Gastrointestinal hemorrhage	Died undelivered
33*	11	Tracheobronchitis and atelectasis	Induced premature delivery with neonatal death

*Autopsy.

TABLE VI. MATERNAL MORBIDITY

TRIMESTER	NO. OF SURVIVORS	HOSPITAL DAYS	
		MEAN	S.E. OF MEAN
First and second	32	58.9	± 13.5
Third	13	89.1	± 20.9

TABLE VII. RESULTS OF FIFTY-ONE PREGNANCIES

TRIMESTER	NO. OF CASES	ABORTIONS	DELIVERIES	STILL PREGNANT	DIED UNDELIVERED	STILLBIRTH	NEONATAL DEATHS
First	14	6	7	1			
Second	20	1	18	1			1
Third	17		15		2	1	3
Total	51	7	40*	2	2	1	4

*Twenty-seven of these patients were delivered elsewhere.

As there was a larger number of deaths and a greater number of respirator cases in the third trimester we compared the morbidity of the survivors in this group with that of the survivors of the first two trimesters by considering the length of stay in the hospital. Table VI summarizes the results. Although the mean length of hospital stay was longer for cases in the third trimester, the scatter of results was so great that there was no statistically significant difference between the groups when the standard errors of the means were compared.

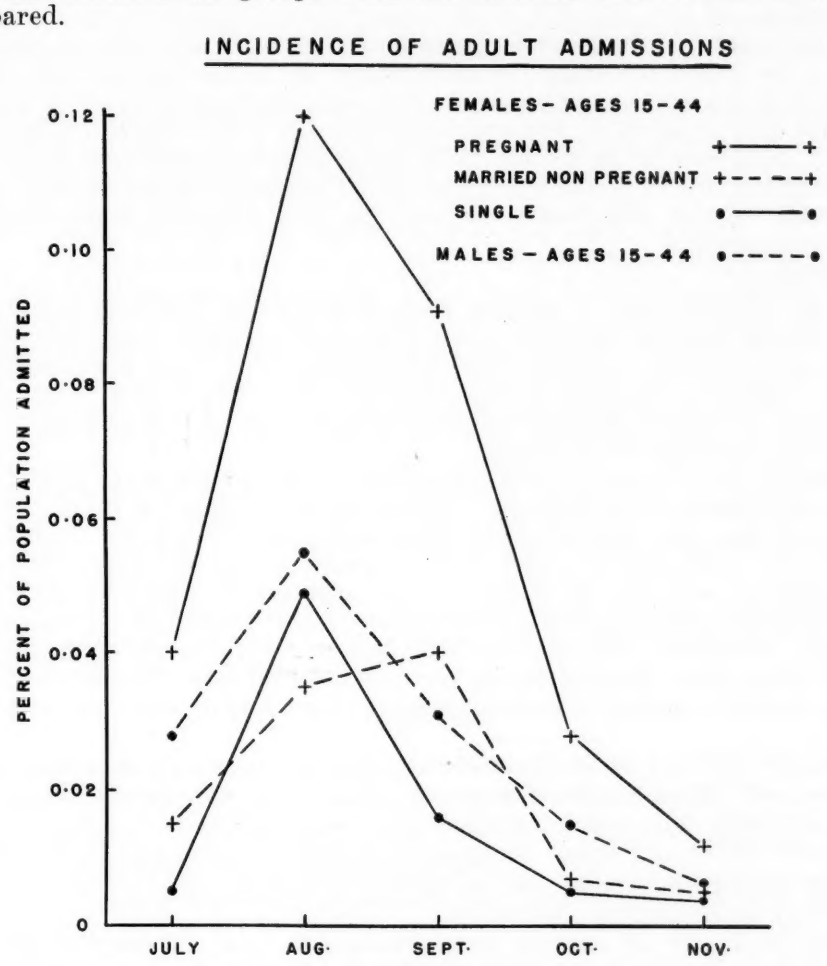

Fig. 2.

The Effect of Pregnancy on Respiration.—

It might be expected that the pregnant uterus, particularly near term, would further embarrass respiratory function in a patient with respiratory paralysis. Indeed, it has been suggested that immediate termination of the pregnancy by cesarean section is indicated in such cases.[1, 4, 11, 12] We have not found that pregnancy seriously interferes with the management of respiration. These patients were adequately ventilated in a tank respirator and, although we made no measurements immediately before and after delivery, we were not impressed that any improvement in respiratory function followed delivery. Of the 5 patients delivered in respirators, 3 still required respirator help for varying periods of the day six to nine months after delivery. The other 2 remained in respirators until they died eight and six days after delivery.

The Effects of Poliomyelitis on Pregnancy

The experience of others[4, 11] indicates that poliomyelitis has little, if any, influence on the course of the pregnancy. The results of the 51 pregnancies reported here are shown in Table VII. The abortion rate, the conduct of labor in spinal cases and in respirator cases, and the possibility of neonatal infection merit some comment.

Abortions.—

Seven of the 51 pregnancies terminated by abortion. Six of these occurred in the hospital during the acute stage of the disease and one patient aborted after the acute stage when she had been discharged from the hospital. This gives an incidence of one abortion for every 6 live births (Table VII). This may represent an increased incidence of abortion compared to the generally accepted rate of one in every 5 to 10 live births, particularly as 37 of the 51 pregnant women admitted were past the first trimester when they contracted poliomyelitis.

Deliveries.—

Of the 40 deliveries, 2 patients were uneventfully delivered prior to admission to this hospital but after contracting poliomyelitis (Cases 28 and 48); 25 have been confined by their own obstetricians after they were discharged from the hospital. We have information that labor was normal in all except one who had a cesarean section for obstetrical reasons. The remaining 13 were delivered by one of us (W. J. McC.).

Cases 12, 19, 37, and 45 had low spinal paralysis and were in the acute stage of the disease when delivered. There was no evidence of uterine inertia. On the contrary, the first stage of labor was probably shorter than normal although the exact time of onset in these patients was sometimes difficult to judge. Special care was given the bladder and bowel as patients with acute low spinal poliomyelitis usually have urinary retention and are prone to fecal impaction. Similarly, the poliomyelitis had no obvious effect on the third stage of labor either in duration or amount of blood loss. The second stage, however, usually required assistance because of the loss of voluntary expulsive force.

Cases 5, 8, 27, and 41 had extensive residual spinal paralysis and delivered after the acute phase of the disease was past. Case 41 had a pre-eclamptic toxemia and was delivered six weeks prematurely with low forceps. Case 27 had a transverse lie which was managed by internal version and breech extraction. The remaining two had normal spontaneous deliveries at term.

Delivery in Respirator Patients.—

Cases 10, 17, 33, 36, and 43 were confined in tank respirators. Four of them were in the acute phase of the disease and three had tracheotomies. Emerson dome respirators were used to allow the patient to be ventilated by intermittent positive pressure while the tank was open. Delivery was carried out as on a flat table or bed. Case 36 was a high spinal case without bulbar involvement who came to term after the acute phase of the poliomyelitis had subsided. Considerable difficulty was encountered with this case as the table could not be dropped to allow the usual method of breech delivery, nor could the patient be turned into the lateral position. If one were faced with this situation again two possibilities would be considered: either a cesarean section in the respirator or the use of an anesthetic machine to maintain ventilation on a proper table.

The question of terminating the pregnancy prematurely is exemplified by Case 33. The patient had marked abdominal distension due to ileus and her condition was steadily deteriorating. The 32 week fetus was viable. The

membranes were ruptured, a short labor ensued, and a 2½ pound premature infant was delivered that died a few days later. The mother subsequently died of respiratory complications (Table III).

Infants.—

There was a total of 40 infants born after the period of viability had been reached (Table VII). Thirty-five of these were live, healthy babies and up to the present time there have been no signs of paralysis. Those born in the hospital while the mothers were still in the acute stage of the disease were immediately transferred to another hospital, out of the poliomyelitis environment.

In Case 19 the fetal heart could not be heard after three hours of labor. The membranes had not ruptured, nor was the cervix dilated at this time. After a labor of 10 hours a stillborn infant was delivered. An autopsy was performed but evidence of intrauterine asphyxia was the only finding.

Four of the infants died within the first two weeks of birth. Case 33 has already been mentioned. Case 15 had recovered from nonparalytic poliomyelitis several months before labor which began in the thirty-second week of pregnancy. She was delivered in another hospital and the infant died of prematurity. Case 26 was delivered at term one month after the onset of poliomyelitis. The infant lived only a few hours and postmortem examination revealed a congenital abnormality of the heart incompatible with life. In Case 48 the mother went into labor at the same time as the symptoms of acute poliomyelitis became evident. She was delivered in another hospital and immediately transferred to our acute poliomyelitis ward. The infant remained in the other hospital where death occurred nine days later. Although the evidence is not conclusive, this infant may have died of acute poliomyelitis, presumably contracted during labor.

Two other infants were lost at term when the mothers died undelivered (Cases 31 and 32). Autopies were carried out on both infants. No evidence of poliomyelitis was found in either.

Summary

1. The proportion of pregnant women admitted to the hospital with acute poliomyelitis was found to be significantly higher than the proportion of other adult groups admitted. This probably represents an increased susceptibility of pregnant women to the disease.

2. Of 51 cases admitted, 14 were in the first, 20 in the second, and 17 in the third trimester.

3. The over-all mortality rate in the pregnant women is very similar to that in other adults of comparable age groups. There was one death in each of the first two trimesters and four in the third.

4. A comparison of length of hospital stay suggests no significant increase in morbidity in the third trimester compared with the first two.

5. The management of respirator cases was not complicated by the presence of a pregnant uterus at term.

6. There were 7 abortions and 39 live births. This may be somewhat higher than the usual incidence of abortion.

7. The first and third stages of labor are not appreciably affected by poliomyelitis but in cases with low spinal paralysis assistance is usually required in the second stage.

8. Delivery in a respirator is not difficult with uncomplicated vertex presentations. The delivery of patients with abnormal presentations in respirators is discussed.

9. Fetal wastage in the series was 14 out of 51 pregnancies. One infant died nine days post partum with some evidence of poliomyelitis. There was no case where the poliomyelitis virus seemed to pass the placental barrier.

Addendum.—Since this paper was submitted for publication, a paper has appeared by J. S. Hunter and C. H. Millican (Obst. & Gynec. 4: 147, 1954) which corroborates the conclusions expressed here.

We acknowledge with pleasure the help of Dr. F. E. Whitworth of the Federal Department of Health, Ottawa, whose advice on the statistical analyses was invaluable. Dr. M. Bowman, Department of Health and Welfare, Province of Manitoba, provided us with the poliomyelitis statistics for the province. We are indebted to the Department of Vital Statistics, Province of Manitoba, for the population statistics and the records of live births. We are also grateful to Dr. A. Schaberg for reports on the autopsy examinations.

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INVERSION OF THE PUERPERAL UTERUS*

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(From St. Joseph's Hospital)

INVERSION of the puerperal uterus is among the rarest of obstetrical complications. It is a complication which occurs but few times during the professional life of even the most experienced of obstetricians. Nevertheless, because of its seriousness, obstetricians must be constantly alert to its possible occurrence and informed as to the most effective method of therapy.

The purpose of this paper is to report fourteen hitherto unrecorded instances of this complication, the first of which occurred in a personal case.

Cases Reported

(Personal Case) S.J.H. No. A-80812.—A 19-year-old primigravid white woman was admitted to the obstetrical service of St. Joseph's Hospital at 6:20 A.M. on July 15, 1953. Her expected date of confinement was July 1, 1953, and upon admission to the hospital she was in early active labor. The fetal heartbeat was audible, the membranes were intact, the cervix was 1 to 2 cm. dilated, half effaced, and the presenting vertex was stationed 1 cm. above the spines. At 10:00 A.M. the patient received Tuinal, 3 grains, and one hour later Demerol, 100 mg., and hyoscine, 1/150 grain. At 4:10 P.M. the patient was delivered of a term-sized infant by elective low forceps and a left mediolateral episiotomy, under open ether anesthesia. At 4:20 P.M. the supervising nurse noted and commented on a "dimpling" of the uterine fundus in the region of the right cornu. At 4:35 P.M. the placenta was delivered by "considerable traction and suprafundic pressure."

Following delivery of the placenta the fundus was noted as soft and boggy and could not be made to contract with oxytocics, and there was considerable vaginal bleeding. A transfusion of 500 c.c. of group O, Rh-negative blood was started. A sterile pelvic examination for the source of bleeding revealed an oozing, firm mass just inside the fully dilated cervix. This was thought by the attending physician to be a pedunculated submucous fibroid as the placenta had apparently been intact on delivery.

The patient was seen in consultation at 6:30 P.M. at which time the systolic pressure varied from 40 to 60 and the diastolic could not be detected. The pulse rate was over 190. The uterine fundus could not be palpated abdominally, and the patient was in deep surgical shock and bleeding with moderate severity. Sterile pelvic examination revealed the fundus completely inverted through the cervix, the latter being soft and about 8 cm. dilated. A second transfusion was started, both bottles being administered under pressure, and gentle efforts were made to reduce the inversion by taxis. A cyclopropane, nitrous oxide, and oxygen mixture was administered to control the patient's restlessness. With the inverted fundus grasped in the palm of one hand, and deep suprafundic pressure exerted with the other, no difficulty was experienced in replacing the fundus. Following this successful maneuver the fundus was massaged gently between the vaginal and abdominal hands, until with the aid of Pitocin, 1 c.c. intramuscularly, and ergometrine, 0.25 mg. intravenously, it was judged to be quite firm. For one hour following reposition, the patient continued to receive whole blood, and then plasma under pressure and oxygen by mask. Her postpartum course was uneventful and she was discharged from the hospital on the seventh postpartum day.

*Presented at the Tenth Annual Meeting of the Society of Obstetricians and Gynaecologists of Canada, Harrison Hot Springs, B. C., June 11 to 13, 1954.

TABLE I. SUMMARY OF CASES REPORTED

CASE	AGE	GRA-VID-ITY	PAR-ITY	DELIVERY	PLACENTA	TIME OF RECOGNITION	ANESTHETIC	THERAPY	RESULT	REMARKS
MS* 9621	18	iii	ii	Spont. R.M.A.	Spont.	Stat.	Spinal	Manual replacement Packed	Recovery	Uterus inverted with the placenta attached
HGH† 2784	24	ii	ii	Spont.	Traction Pressure	20 minutes	Ether	Manual replacement	Died	Not transfused
HGH A-38781	20	i	i	(Elective low forceps)	Traction Pressure	Stat.	Ether and chloroform	Manual replacement	Recovery	Home delivery; one subsequent uneventful pregnancy
HGH A-21755	35	i	i	E.L.F.	Spont.	2¾ hours	Ether	Manual replacement with cyclopropane	Recovery	One subsequent uneventful pregnancy
HGH A-28037	20	i	i	E.L.F.	Pressure	70 minutes	Ether	Manual replacement Packed	Recovery	Two subsequent uneventful pregnancies
HGH A-20186	27	ii	ii	Spont.	Spont.	15 minutes	Ether	Packed Manual replacement	Recovery	Sterilized five years later; indication?
HGH A-28464	23	iii	ii	E.L.F. L.O.P.	Traction Pressure	60 minutes	Ether	Manual replacement Packed	Recovery	Puerperal parametritis and thrombophlebitis. Complete amenorrhea after
HGH A-73547	27	i	i	E.L.F.	Spont.	25 minutes	Ether	Manual replacement with cyclopropane	Recovery	Epinephrine hydrochloride prior to manual replacement
SJH‡ 390	19	i	i	E.L.F.	Credé	30 minutes	Ether	Spinelli operation	Died	Not transfused. In shock when therapy instituted
SJH 1373	19	ii	i	E.L.F.	Pressure	6 hours	Ether	Manual replacement Packed	Died	Not transfused. Shock irreversible when replaced
SJH 3038	30	i	i	Spont.	Spont.	2½ hours	Ether	Vaginal packing	Died	Not transfused
SJH 195	24	i	i	Spont.	Spont.	6 weeks	Ether	Vaginal hysterectomy	Recovery	
SJH A-19603	33	i	i	Spont. R.S.A.	Spont.	Stat.	Ether	Vaginal packing	Recovery	Uterus inverted with the placenta attached
SJH§ A-80812	19	i	i	E.L.F.	Traction Pressure	2 hours	Ether	Manual replacement	Recovery	

*Mountain Sanatorium, Hamilton, Ont.
†Mount Hamilton Division, Hamilton General Hospital.
‡St. Joseph's Hospital, Hamilton, Ont.
§Author's Case.

In addition to this one personal case, 13 others have been uncovered in the records of the three hospitals in Hamilton in which obstetrical work is done. These cases are shown in Table I and summarized in Table II.

TABLE II. SUMMARY OF PERTINENT DATA IN FOURTEEN CASES OF INVERSION OF THE UTERUS

Total cases	14	
Incidence	1/4,753	
Parity:		
Primiparas	9	(71.4%)
Multiparas	5	
Etiology:		
Spontaneous	7	(50%)
Traction and/or pressure	7	
Symptoms: Shock and hemorrhage in all except one case		
Recognition:		
Immediate to 6 weeks		
11 recognized in the first three hours		
Anesthesia:		
Spinal	1	
Ether	12	
Chloroform and ether	1	
Therapy:		
Immediate manual reposition on recognition	11	
Spinelli procedure	1	
Vaginal hysterectomy	1	
Vaginal packing, inversion not recognized	1	
Mortality	4	(28.6%)
Remarks:		
4 subsequent pregnancies in three patients, all uneventful.		
4 deaths occurred in 1924, 1929, 1930, and 1932; patients were not transfused		

Definition and Classification

Inversion of the puerperal uterus means the accidental turning inside out of the pregnant uterus during the third stage of labor, or immediately thereafter. This may occur to greater or lesser degree following either normal or abnormal labor. Inversion of the uterus may also of course occur as a gynecological complication of pedunculated myoma, carcinoma, sarcoma or other abnormal masses within the uterine cavity, but such cases are not considered as a part of this report. Also excluded is one case of "intentional inversion," where the consultant obstetrician purposely inverted, under deep inhalation anesthesia, a puerperal uterus late in the third stage of labor for a partial placenta accreta, following the successful removal of which the uterus was reposited without immediate or delayed sequelae to the patient.[1]

For purposes of classification, that proposed by Kellogg[12] leaves little to be desired, namely: (1) acute inversion: inversion accompanied by more or less complete cervical dilatation; (2) subacute inversion: inversion followed by firm cervical constriction; (3) chronic inversion: inversion of more than four weeks' duration.

This classification may be further modified by classifying inversion as complete or incomplete, depending upon the extent to which the fundus of the uterus has become turned inside out.

Etiology and Incidence

The belief is generally expressed that inversion is due to poor management of the third stage of labor, and reflects bad judgment on the part of the attendant in the exercise of too vigorous methods of expression of the placenta, either by suprafundic pressure, traction on the umbilical cord, or manual removal.[6] That this is only partially true is shown by such reports as that of Das,[8] who noted that among 297 collected cases of puerperal inversion, 40 per cent were spontaneous in occurrence. Harer and Sharkey[11] reported 24 per cent of their cases to be spontaneous and unavoidable. Bell and his associates[3] found 29 per cent spontaneous. In the present report 50 per cent are described as of spontaneous occurrence, and not preventable.

Unquestionably, overly ambitious efforts to deliver the placenta are of etiological importance, but almost equally obvious is the fact that inherent factors within the uterine musculature play an important predisposing role. Although many such factors are listed in the literature (chronic metritis, coexisting fibroids, etc.) the most significant seems to be the natural thinning and relaxation of the uterine musculature at the side of the placental attachment.[14]

Schaefer and Veprovsky[15] have grouped the causes of inversion under predisposing and exciting causes. They list as predisposing factors those which weaken the uterine wall or leave it in a relaxed and atonic state (e.g., adherent placenta, failure of proper innervation, frequent pregnancies, tumors, and inertia). Under exciting causes they list (1) manual removal of the adherent placenta, (2) increase in intra-abdominal pressure (coughing, vomiting, straining, etc,), (3) mismanagement of the third stage of labor: (a) improper fundal pressure, (b) traction on the umbilical cord, (c) injudicious use of oxytocic drugs.

Phaneuf[14] felt that any of these factors might result in simple indenting of the fundus, which in itself is productive of a chain of events which he described as follows: "After any portion of the uterus becomes indented to a considerable extent the rest of the organ seizes this invaginated portion as it would a foreign body, and in attempting to expel it, turns itself inside out."

Figures regarding incidence and mortality are in reality of little value, except to illustrate the rarity of the condition. Among the reported rates of occurrence are the two extremes of 1 in 250,000 cases,[2] as compared to 1 in 740 cases.[11] Eastman, from the Johns Hopkins Hospital, reported an incidence in that clinic of 1 in 20,000 deliveries, but the majority of figures for incidence are more in accord with those of Cosgrove[6] and Schaefer[15] who reported incidences, respectively, of 1 in 4,333 cases and of 1 in 6,433 cases. The cases reported here represent an incidence of 1 in 4,753 cases.

The mortality of 29 per cent noted in this series is in general keeping with most recorded figures, which have varied between 15 and 40 per cent. That these figures may not be valid today is suggested by the fact that the 4 recorded deaths in the present series occurred in the era prior to liberal use of transfusions and antibiotics.

Signs and Symptoms

The classical manifestations of inversion are surgical shock, usually of sudden onset and marked degree, and hemorrhage of varying degree, but usually profuse. Dimpling of the fundus should immediately suggest inversion, yet it is not always recognized for its true significance as in the personal case reported.

Inability to palpate the fundus suprapubically should at least arouse immediate suspicion. The somewhat amusing incident is related by one of our senior colleagues[17] about one of his obstetrician friends in a neighboring Canadian city. The obstetrician concerned was complacently awaiting the spontaneous delivery of a placenta when the attending anesthetist exclaimed in surprise and chagrin that the uterine fundus has suddenly disappeared from his grasp. The shock of the obstetrician far surpassed that of his patient but his recovery was spontaneous and immediate and he was able to replace the inverted mass in the vagina in a matter of seconds without any obvious effect upon the patient.

That severe shock and hemorrhage do not always accompany inversion is demonstrated by one of our cases (S.J.H. 195) in which the diagnosis was not made until six weeks postpartum when the inverted, septic uterus was found wholly occupying the vagina. The patient's major complaint was that of moderate bleeding when she attempted to douche.

The diagnosis is certain only when the complete or partially inverted uterus is found on vaginal examination.

Therapy

The treatment of puerperal inversion of the uterus by immediate replacement seems simple and obvious. That this is not the case is apparent from the divergence of expressed views on therapy and the number of methods suggested. These opinions regarding the timing of reposition vary from immediate intervention[3, 4, 5, 6, 9, 11] to complete disregard of the inversion and management of the shock and hemorrhage, to be followed by reposition days to even months later.[13] Suggested methods of therapy vary from simple manual reposition to abdominal intervention and vaginal hysterectomy.

It is obvious that an obstetrical emergency, the state of which is influenced by such variable factors as degree of shock and hemorrhage, time of recognition, degree of cervical dilatation, presence or absence of infection, and coincidental uterine pathology cannot be handled in any one simple, dogmatic way.

From the reports of the majority of writers, it is apparent that there is wide acceptance of a plan of immediate replacement in the acute stage. The most obvious measure to combat shock is certainly early replacement of the hemorrhaging inverted uterus. This, of course, does not imply that immediate transfusion of whole blood or blood plasma is in any sense to be disregarded.

Although immediate replacement is generally recommended, there is a divergence of views on the method of procedure, which may vary from simple manual replacement to abdominal intervention in the form of the Huntington procedure.[12, 14] Where extensive, traumatic manipulation of the inverted

uterus is not required, immediate manual reposition is the method of choice. When such an attempt is unsuccessful then abdominal replacement becomes necessary.

It is in the presence of firm cervical constriction, characterizing Kellogg's subacute type, that one is justified and even more or less obligated to disregard the inversion because of the futility and trauma, and the further shock that would be produced by persistent efforts at manual reposition. Here the institution of vigorous measures to combat shock is of paramount importance, combined with the packing of the vagina to control bleeding from the inverted fundus. Once this has been done and the patient is considered a suitable operative risk, the uterus may then be replaced by the Huntington procedure through the abdominal route. Various methods have been suggested for relaxing the constricted cervix, such as the use of epinephrine hydrochloride[7] and other antispasmodics, but the efficacy of these agents is open to serious question.

Chronic uterine inversion is the rarest of the three types encountered and is generally found as a complication of coexisting gynecological pathology. Hemorrhage and shock are usual, the patient being more likely to complain of a foul leukorrhea, persistent vaginal bleeding, and pain. With this type sepsis of the inverted fundus becomes much more of a factor to be controlled; the uterus may become gangrenous, due to the strangulation of the blood supply by firm contraction of the cervix about the inverted mass. Management of the chronic stage consists primarily in the control of infection, following which the uterus may be reposited by the Spinelli method of incising the constricting cervix and the lower uterine segment anteriorly and then replacing the fundus. This method of treatment has been more popular on this continent than the Haultain operation, in which the abdomen is entered, the constricting cervical ring is incised posteriorly, the fundus drawn up into the abdomen and then the cervical incision closed. In some cases of chronic inversion, depending on the parity of the patient and the state of the inverted uterus, vaginal hysterectomy may become the method of choice.

Summary and Conclusions

Inversion of the puerperal uterus is a rare and serious complication of obstetrics which occurs approximately once in every 5,000 deliveries and is accompanied by a relatively high mortality rate. The principal signs are hemorrhage and shock. The hemorrhage is usually profuse and the shock sudden and severe. Occasionally, however, both signs may be absent and the inversion of the uterus may be discovered entirely by accident.

Although inversion may occur spontaneously, nevertheless suprafundic pressure, Credé expression of the placenta, traction on the umbilical cord, and manual removal of the placenta are important predisposing factors.

In any case of postpartum hemorrhage, inversion of the uterus must be considered a possible cause. We feel this is particularly true following deep inhalation anesthesia, when the uterus is left in a flaccid and atonic state fol-

lowing delivery of the infant. The prognosis is directly related to the time interval between the occurrence of the inversion and its recognition, the degree of shock and hemorrhage, and the rapidity with which measures to combat shock are instituted. Bell and associates[3] have shown that immediate recognition offers the best chance of survival, regardless of the type of treatment given, and that the mortality rate, which he found to be 17.0 per cent, seems to rise steadily as recognition is delayed up to the point of about 48 hours, and beyond this time patients who have unrecognized inversion show an improved mortality, presumably due to control of the hemorrhage by cervical contraction.

If the condition is recognized prior to firm cervical constriction, treatment should consist of immediate antishock measures and the manual replacement of the inverted fundus by taxis.

Where cervical constriction has occurred, precluding manual reposition, or where gentle efforts at manual replacement by taxis fail in the absence of cervical constriction, the inversion itself should then be considered secondary and all therapy directed toward correction of blood loss and shock. Once this has been accomplished operative replacement should be carried out, the Huntington procedure being the method of choice.

Chronic inversion following control of infection is best treated by operative replacement as in the Spinelli procedure or the Haultain method. Some cases of chronic inversion are, however, best treated by vaginal hysterectomy.

Following manual replacement of the fundus of the uterus it should always be examined for rupture.

Recurrence of inversion, either immediately following replacement or in a subsequent pregnancy, is rare, and pregnancy in a fundus that has been inverted is almost invariably uneventful.

I wish to acknowledge the kind assistance of Rev. Sister Marita and Miss Lillian Johnston of the record departments of St. Joseph's Hospital and the Hamilton General Hospital, respectively, in the preparation of this report.

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FIVE-YEAR ANALYSIS OF BREECH DELIVERIES*

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THIS series embraces 386 breech deliveries on the Obstetrical Services of the Montreal General Hospital and the Catherine Booth Hospital, Montreal, during the years 1949 to 1953, inclusive. The Montreal General Hospital is a closed hospital and 99 of the patients were delivered there, all by qualified obstetricians; while at the Catherine Booth Hospital, which is open, 41 per cent of 287 deliveries were performed by qualified obstetricians, 31 per cent by the Courtesy Staff of general practitioners, and 28 per cent by junior rotating interns. In both hospitals it is the practice to treat all cases individually and in the majority conservative treatment is carried out.

The management of breech delivery has been the subject of a number of articles in the last few years.[1-9, 12] In the Montreal General Hospital and the Catherine Booth Hospital, the following principles have been observed in the management of the cases in this series:

The onset of labor should be spontaneous and the membranes are kept intact, if possible, until delivery is imminent. If the mother's condition remains good and labor is progressing satisfactorily, without any signs of fetal distress, we allow the hips of the baby to deliver spontaneously, and then, under anesthesia, we guide the shoulders and head through the birth canal. Piper forceps are used to deliver the aftercoming head whenever the slightest difficulty occurs. Episiotomy is performed in the majority of these cases, in order to avoid unnecessary trauma to the baby and also to shorten the second stage of labor. Decomposition and extraction of the breech is resorted to only if there is lack of progress or signs of maternal or fetal distress. Potter has stressed the importance of full dilatation of the cervix prior to breech extraction and we thoroughly endorse that statement.

We advocate the use of general anesthesia for all breech deliveries, and deep anesthesia if decomposition and extraction are necessary. Because of the shortage of trained anesthetists, however, a large number of our patients have been delivered under Trilene. While this type of anesthesia does not provide as much relaxation as is desirable, it is a safe anesthetic in untrained hands and we can find no evidence of increased fetal loss as a result of its use.

We were unable to ascertain how often external version was attempted in this series, but we feel very strongly that it is an important procedure in attempting to reduce fetal mortality. Harrison[5] showed conclusively that by external version he had reduced his fetal mortality.

*Presented at the Tenth Annual Meeting of the Society of Obstetricians and Gynaecologists of Canada, Harrison Hot Springs, B. C., June 11 to 13, 1954.

General Considerations

During the five-year period 1949-1953, there were 12,432 deliveries of which 386 were breech deliveries, or 3.2 per cent (Table I). Fifty-three patients had twin pregnancies in which one or both babies were delivered as a breech, an incidence of 13.7 per cent.

TABLE I. THE INCIDENCE OF BREECH DELIVERIES

AUTHOR	NUMBER OF DELIVERIES	PER CENT
Moore and Steptoe[8]	51,571	2.8
Cannell and Dodek[1]	16,166	3.4
Waters[16]	20,000	4.3
Patton and Mussey[10]	6,195	4.8

The parity of the patients studied is given in Table II. The figures show that the number of primiparas in the series was only slightly in excess of the number of multiparas. Zacharias and Heery[18] in a previously reported series gave their proportion of primiparas to multiparas as 273 to 611, and Ware, Winn, and Schelin,[13] 192 primiparas to 98 multiparas.

TABLE II. PARITY

Primiparas	208	(54%)
Multiparas	178	(46%)

Frank breech delivery was the most common type encountered and was found in 148 primiparas and 104 multiparas (Table III).

TABLE III. TYPE OF BREECH AND PARITY

	FRANK	FOOTLING	COMPLETE	UNSPECIFIED	TOTAL
Primiparas	148	49	5	6	208
Multiparas	104	62	7	5	178
Total	252	111	12	11	386

Methods of Delivery.—Spontaneous and assisted breeches were those deliveries in which the hips were allowed to deliver spontaneously. The shoulders and head were then guided through the birth canal and breech extraction or operative interference was begun before the passage of the breech over the perineum (Table IV). Cesarean section was used in elderly primiparas, in cases of fetopelvic disproportion, and in certain cases of inertia. Piper forceps were used to deliver the aftercoming head in 153 cases, an incidence of 40 per cent.

TABLE IV. TYPE OF DELIVERY

Spontaneous and assisted	216
Breech extraction	147
Cesarean section	15
Type of delivery unspecified	8

TABLE V. REASONS FOR INDUCTION OF LABOR

False labor	4
Toxemia	8
Postmaturity	4
Prolonged rupture of membranes	3
Twin pregnancy	2
Rh-negative mother with immunization	1
Fetal abnormality	1
Unspecified	6
Total	29

Labor was induced in 29 patients, 8 per cent. The various reasons for induction are given in Table V.

Cesarean section was performed on 15 patients, an incidence of 3.9 per cent (Table VI). This incidence is similar to the over-all cesarean section rate in the two hospitals.

TABLE VI. INDICATIONS FOR CESAREAN SECTION

Elderly primipara	6
Inertia	3
Abruptio placentae	1
Fetopelvic disproportion	1
Toxemia of pregnancy	2
Previous cesarean section	1
Central placenta previa	1
Total	15

Characteristics of Labor.—Premature rupture of the membranes was encountered in 84 patients, 22 per cent for the series. Other associated conditions affecting labor are shown in Table VII.

TABLE VII. ASSOCIATED CONDITIONS

	NUMBER	PER CENT
Toxemia of pregnancy	52	13.5
Postpartum hemorrhage	24	6.2
Placenta previa	2	0.5
Twin pregnancies	53	13.6
Premature rupture of membranes	84	22
Prolonged rupture of membranes	20	5.3

The average length of labor was 11 hours, 28 minutes for the primiparas and 7 hours, 54 minutes for the multiparas.

Fetal Results.—There were 79 premature deliveries in this series in which there were 31 fetal deaths, 39.3 per cent. In the 307 full-term deliveries, there were 13 fetal deaths, 4.2 per cent. Four of these deaths may be considered as having been preventable. Three difficult extractions which terminated in fetal death should have been assessed earlier in labor; possibly a cesarean section would have saved the baby. The fourth case was one of a prolapsed cord and a partially dilated cervix in which extraction was done and the baby lost, whereas "masterful inactivity" might have produced a live baby.

TABLE VIII. CAUSES OF FETAL MORTALITY

Prematurity	17
Difficult extraction	3
Toxemias of pregnancy	2
Fetal abnormalities	9
Tentorial tear and subarachnoid hemorrhage	4
Prolapsed cord	3
Premature separation of placenta	3
Cause unspecified	3
Total	44, or 11.4%

TABLE IX. FETAL MORTALITY AND TRAINING OF ACCOUCHEUR

	DELIVERIES	FETAL DEATHS	PER CENT
Trained obstetricians	259	25	9.6
Courtesy Staff	84	10	11.9
Junior interns	41	9	22
Precipitate deliveries in bed	2		

When fetal mortality is considered in relation to the variously trained accoucheurs who carried out the deliveries, it will be seen that fetal deaths were fewer when trained obstetricians were in charge (Table IX).

Maternal Morbidity.—Fifteen (4.0 per cent) of the mothers were morbid. Intrauterine infection was the chief cause of maternal morbidity (Table X).

There were no maternal deaths.

TABLE X. CAUSES OF MATERNAL MORBIDITY

Intrauterine infection	10
Pyelonephritis	2
Bronchopneumonia	2
Thrombophlebitis	1

Summary and Conclusions

There were 386 cases of breech presentation in 12,432 deliveries during the period 1949-1953.

In this series there were 23 stillbirths and 21 neonatal deaths, an uncorrected fetal mortality of 11.4 per cent. There were 9 babies with fetal abnormalities, incompatible with life. When these are deducted, the corrected fetal mortality is 9 per cent. In our series, prematurity was the chief cause of fetal death.

The incidence of prematurity in cephalic presentations is much lower than in breeches. Therefore, it is suggested that external versions should be attempted as a routine procedure. This question is controversial, and deserves very careful consideration, as there are dangers of complications. It can also be pointed out that the earlier the version is carried out the greater is the chance of reversion to a breech presentation.

One cannot stress too much that the cervix must be fully dilated and paralyzed before delivery is attempted, since a nonretracted cervix may contract around the baby's neck and shoulders, causing great difficulty in delivering the head.

Piper forceps should be used to deliver the aftercoming head almost routinely to avoid pull on the baby's neck, with consequent injury to the head. Episiotomy before delivery of the breech reduces trauma to the baby, and cuts down fetal mortality.

Speed is not necessary in the delivery of a breech. Steady, gentle traction should be used in the assisted delivery. The baby's back should be rotated in such a manner as to aid in the delivery of the arms, and to prevent the chin from rotating under the symphysis.

It appears that the results were better when the delivery was carried out by a qualified obstetrician. Therefore, it is suggested that consultation in breech cases be made obligatory in all open hospitals.

There were two fetal deaths which were definitely due to inexperience and were, therefore, preventable. X-ray pelvimetry is strongly advocated, particularly when a frank breech is suspected.

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FETAL LOSS IN TORONTO FOR ONE YEAR*

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THIS preliminary report covers the initial eleven months of a proposed five-year survey of stillbirths and neonatal deaths in the city of Toronto. Such a study appears important, for, although maternal mortality has been materially reduced in the past twenty years, fetal mortality has not been reduced to the same extent. In one of the hospitals surveyed in this study, the neonatal mortality of premature infants has indeed remained substantially unchanged for many years.

The primary purpose of this investigation is to determine accurately the extent of fetal wastage and to examine the factors involved in its occurrence. It is hoped that, from the information obtained, methods may be evolved to reduce fetal loss to a minimum.

Organization of the Project

The project is supported by a National Health Grant through the Government of Ontario. A qualified obstetrician, pediatrician, and pathologist comprise the team.

In cases of stillbirth or neonatal death, it is the duty of the obstetrician to obtain immediately data on all pertinent factors in the prenatal course of the mother and details of labor and delivery. A prompt interview with the responsible physician is important. The pediatrician examines and follows the course of all babies whose survival is in doubt and of those infants in whom complications have developed. The pediatrician is in charge of the neonatal ward of the Hospital for Sick Children and supervises the treatment of the babies referred there on discharge from the obstetrical units. None of the obstetrical divisions has a pediatric ward. The pathologist, whose work is limited to obstetric pathology, performs the autopsies on infants in two hospitals, attends those in the other hospitals, and sees that the special requirements of fetal postmortem examinations are fulfilled. It was found that previously many of the examinations required for this type of survey had not been done routinely.

Clinical Material.—All patients delivered in the public wards of six Toronto hospitals comprise the material studied. Four of these hospitals are affiliated with the University of Toronto and are "teaching hospitals." All six maintain prenatal clinics and have control of most of their patients

*Presented at the Tenth Annual Meeting of the Society of Obstetricians and Gynaecologists of Canada, Harrison Hot Springs, B. C., June 11-13, 1954.

throughout a portion of their prenatal course, labor, delivery, and postpartum period. A small proportion of these are not "booked cases." The project has been confined to clinic patients as a small, well-conducted, pilot scheme was believed to be of greater value than a larger, more poorly controlled study involving many difficulties with private patients and their records. Further, the autopsy rate on babies of private patients is very low. In the largest hospital studied, for example, the autopsy rate on the private service is 8 per cent, whereas that on the public service is 88 per cent. To date, in this survey, 82 per cent of the infants who were stillborn or died in the neonatal period have been subjected to complete postmortem examinations. It is realized, of course, that the fetal wastage in a selected economic group in the community is being studied and that it represents only about 25 per cent of the births in these hospitals.

Preliminary Findings.—Table I shows the fetal loss in the six hospitals studied.

There were 4,294 confinements on the public wards with 147 stillbirths and neonatal deaths, a gross fetal loss of 3.4 per cent. The city of Buffalo's rate of 2.8 per cent includes private cases which may tend to improve their results. The state of New York's rate of 3.2 per cent, however, should provide a better basis for comparison though it includes births in the home, whereas ours were hospital deliveries in favorable surroundings. The 2.9 per cent rate in British Columbia is the lowest achieved in any Canadian province up to this time.

TABLE I. FETAL LOSSES IN THE PUBLIC WARDS OF SIX TORONTO HOSPITALS, JULY, 1953, TO JUNE, 1954

Total fetal loss	147
Total live births	4294
Fetal loss for series	3.4%

The fetal loss for the individual hospitals is depicted in Table II.

TABLE II. FETAL LOSS, INDIVIDUAL HOSPITALS*

HOSPITAL	1	2	3	4	5	6
Stillbirths.—						
Term	11	2	5	3	5	2
Premature	6	7	3	0	1	3
Neonatal Deaths.—						
Term	8	13	1	4	3	3
Premature	14	9	3	6	5	4
Immature	8	5	5	6	1	1
Total fetal loss	47	36	17	19	15	13
Total live births	1,059	887	807	596	469	476
Premature loss	31%	27%	22%	25%	26%	25%
Immature loss	100%	66%	71%	100%	100%	50%
Per cent total fetal loss	4.4	4.1	2.1	3.0	3.2	2.7

*Hospitals 1, 2, 3, 4, are University of Toronto teaching institutions.

In this study infants are considered to be premature if they weigh between 2½ and 5½ pounds. The immature group are those liveborn babies that weigh between 1 and 2½ pounds. A liveborn infant is one that shows any sign of life such as respiration, heartbeat, or movement of voluntary muscle. It is pointed out that these criteria are a compromise between the standards currently employed in Ontario and those in more general use throughout Canada.

There is no noticeable difference in the types of patients confined in the different hospitals. In an attempt to equalize the factor of the period of gestation, identical records have been kept for surviving prematures and immatures, as well as for prematures and immatures lost. The premature and immature

birth rates vary slightly in the different hospitals. Hospital number 3, with one of the higher immature rates, has the lowest fetal loss. This institution has the most recent building and best physical layout for observation and care of prematures. In addition, it has more new incubators and, even more important, trained and experienced nursing supervision. It has, however, no full-time daily pediatric supervision as has Hospital number 1, where rounds are made by a pediatrician. A study of these figures suggest that the total fetal wastage corresponds closely with the loss of premature or immature infants.

TABLE III. CAUSES OF DEATH IN 147 CASES

Anoxia	20%
Abnormal pulmonary ventilation	18%
Birth trauma	14%
Congenital anomalies	14%
Infection	7%
Rh incompatibility	4%
Toxemia	2%
No demonstrable cause	18%

The causes of fetal death which are shown in Table III, may be briefly commented upon.

Anoxia comprises the largest group. It includes severe degrees of abruptio placentae and prolapse of the cord.

Abnormal pulmonary ventilation, the second largest group, includes those infants with the pathological findings of immature development of lung tissue and hyaline-membrane disease. All were premature or immature infants.

Birth trauma: Intracranial hemorrhage was the principal cause of death in this group. Many of these deaths occurred in premature babies in whom intracranial hemorrhage may occur with much less trauma than in the term infant. It emphasizes the need for greater care in the delivery of the premature infant. Two cases are recorded where the baby was literally blown up by the use of oxygen administered directly from the tank to the intratracheal catheter. As the year progressed, the proportion of those lost from birth trauma decreased considerably. This may be due to increasing experience of the house staff which suggests the need for greater supervision by the attending staff when the annual change in interns occurs.

Congenital anomalies include only those considered by the pathologist to be incompatible with life. Lesser anomalies are listed elsewhere. In no case was a history of any maternal illness or rubella elicited.

Infection as a cause of neonatal death was in most instances a pediatric responsibility. Four deaths occurred where infection of the fetus followed prolonged rupture of the membranes without administration of antibiotics prophylactically, prior to or during labor. There were 28 cases with prolonged rupture of the membranes managed the same way without evidence of fetal infection. We are not convinced that the prophylactic use of antibiotics will prevent fetal infection and have, therefore, not employed them in this manner.

Hemolytic disease of the newborn, or erythroblastosis, accounts for 4 per cent of our fetal loss. We have recently revised our routine in the management of babies born to Rh-isoimmunized mothers in order to speed up performance of the Coombs' test and to shorten the time interval between birth and commencement of replacement transfusion, when indicated. It is hoped, thus, to reduce this mortality. In this city, such babies are not transfused in the obstetrical hospital, but are transferred to the Hospital for Sick Children. Careful organization is required to avoid delay and resultant fetal loss due to delayed treatment.

Toxemia, surprisingly, accounts for only 2 per cent of fetal deaths.

Unexplained deaths include those of which we could not be certain of the cause, either clinically or after autopsy. Cases of prolonged labor with fetal death in which no autopsy evidence of trauma or anoxia was found are included here. There was one baby that weighed over 9 pounds in the 147 that died.

In Table III no attempt has been made to separate stillbirths and neonatal deaths. Obviously, from these findings, the major responsibility for preventable fetal wastage is an obstetric rather than a pediatric responsibility.

The Special Problem of Prematurity

Table IV provides a broad picture of the problem of premature birth. It can be seen that 43 per cent of deaths occurred in small babies. Expressed in another way, we are losing 25 per cent of our liveborn premature infants. Despite recent authoritative reports from Sweden and England, one still encounters individuals who believe that the small baby is not worth saving. This attitude is disturbing and lacks both moral and medical foundation. It is in this large group of small babies that we have some scope for prevention of fetal loss. Conservative management of maternal complications, whenever possible, while the fetus is small and yet unborn, and careful management of labor and delivery are our responsibilities. The importance of medical attendance at the births of small babies is borne out, time and time again, in our study. Many of these are breech presentations with added complications at delivery when unattended. Many infants in vertex presentation, when unattended, suffer traumatic uncontrolled delivery and lack of immediate care including adequate resuscitation.

TABLE IV. DATA ON THE PROBLEM OF PREMATURITY

Frequency of prematurity: 278 births or a rate of 6.4%	
Total loss occurring in prematures	43%
Neonatal loss of prematures	25%
Cause of Premature Labor.—	
Unknown	65%
Maternal complications	27%
Obstetrical interference	8%
Relation of Week of Gestation and Weight to Fetal Loss.—	
Babies mature by date, premature by weight: 40% of group, loss of	3%
Babies premature by date and by weight: 60% of group, loss of	33%

Cause of premature labor is a poor term. A more apt one might be *circumstances associated with premature birth.* In the unknown group, the patients have been questioned closely and only in the occasional case has a possible precipitating cause been uncovered. There are more illegitimate births here than in the mature birth group, a finding noted in other investigations.

The relation of weight and period of gestation to the loss of premature infants is interesting. One group comprising 40 per cent of babies with birth weighs between 2½ and 5½ pounds had according to history periods of gestation of 36 weeks or more. The loss in this group is only 3 per cent. On the other hand, the loss in babies, premature both according to weight and to period of gestation, was 33 per cent. In the mature gestation group there was a larger percentage of heavier babies than in the premature gestation group. Nonetheless, it seems evident that the period of gestation, rather than the weight of the infant, is the important factor in survival. On only two occasions, ill-timed elective interference was responsible for the induction of premature labor and the resultant fetal deaths.

TABLE V. ANESTHETIC AND PREMATURE LOSS IN A GROUP OF 207 LIVEBORN PREMATURE BABIES

ANESTHETIC	LOSS %
Cyclopropane	25
Ether	20
Pudenal block	19
No anesthetic	18
Trilene	15
Spinal	0

The percentage loss in 207 liveborn premature infants has also been tabulated according to the anesthetic employed (Table V). All liveborn prematures have been included here, including those cases in which maternal complications, fetal complications, and complications of labor and delivery have occurred. One might have considered only uncomplicated spontaneous premature births, but if it is felt that general anesthesia may depress respiration in a small infant, it will also do so in complicated cases, and may well be the deciding factor in survival. In one hospital, we have recently begun delivering all prematures under pudendal block or local infiltration. Sedation is withheld in these cases as much as possible after proper explanations to the patient. The anesthetics are administered by junior interns except in one hospital where an attempt has been made to have residents in the Anaesthesia Department give anesthesia to ward patients. Cyclopropane has been given only by more experienced members of the house staff or by juniors who have had their training in anesthesia. It is felt that anesthetic factors cannot be assessed on the basis of the actual agent employed, but depend also on the depth of anesthesia and the skill of the anesthetist. Although the study of our results previously given does not reveal the advantage of any special anesthetic agent, a larger series may produce more definite evidence.

Conclusions

To date, we have achieved our initial object in stimulating interest in the problem of fetal loss and its prevention in both nursing and medical groups in this community. We feel that our tabulations so far are accurate. As the survey continues and larger numbers are collected, the material will naturally be susceptible to more significant and wider statistical and clinical interpretation.

Original Communications

RESULTS OF AN EXPERIMENT IN THE CONTROL OF CANCER OF THE FEMALE PELVIC ORGANS AND REPORT OF A FIFTEEN-YEAR RESEARCH*

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OVER a fifteen-year period, 1938 to 1953, members of the Department of Gynecology at the Woman's Medical College of Pennsylvania have endeavored to determine the value of periodic examination in the control of cancer of the female pelvic organs and breasts. Progress reports have been made earlier,[1] and it will not be necessary to give details of methods of procedure.

Pelvic Cancer

From Jan. 1, 1938, to Dec. 31, 1952, a total of 18,753 pelvic examinations were made on a group of volunteers, white women between 30 and 80 years of age, presumably well (Table I). At the beginning of the investigation the group numbered 1,319. At the end of the research the group numbered 537. Some 57 volunteers died, others moved away, lost interest, or dropped out for other reasons. During the fifteen-year period, 17 pelvic cancers were found.

TABLE I. SUMMARY OF CLINICAL STUDY FROM JAN. 1, 1938, TO DEC. 31, 1952

Volunteers at beginning of investigation	1,319
Volunteers completing investigation	537
Number of pelvic examinations	18,733
Pelvic cancers discovered	17

The exact site of the cancer and the five-year period in which these cancers were detected are shown in Table II. No cancers of the vulva were found and none of the Fallopian tube. Only 2 pelvic cancers were found in Jewish women, both of these in the ovary.

TABLE II. SITE OF EACH PELVIC CANCER DETECTED

	UTERINE CERVIX	UTERINE BODY	OVARY	VAGINA	TOTAL
First five-year period	3	1	0	0	4
Second five-year period	1	1	2	1	5
Third five-year period	0	3	4	1	8
Total	4	5	6	2	17

*Presented at a meeting of the Philadelphia Obstetrical Society, March 4, 1954.

Since marital state and parity are factors in the development of cancer of the uterine cervix and of the uterine body, and since cancer of the uterine cervix is very rare in Jewish women, it seemed important to classify the volunteer group along these lines (Table III).

TABLE III. MARITAL STATUS OF 537 CONTINUING VOLUNTEERS

	TOTAL CASES IN STUDY	PELVIC CANCERS FOUND			
		UTERINE CERVIX	UTERINE BODY	OVARY	VAGINA
Single nulliparous	58				
Jewish	1	0	0	0	0
Non-Jewish	57	0	0	0	1
Married nulliparous	81				
Jewish	7	0	0	2	0
Non-Jewish	74	0	1	1	1
Parous	398				
Jewish	76	0	0	0	0
Non-Jewish	322	4	4	3	0

Nine of the 17 volunteers in whom pelvic cancers were found are alive with no evidence of recurrence. One patient who had cancer of the uterine cervix shows no evidence of recurrence sixteen years after discovery and after treatment by radium. Two others show no recurrence fifteen years after radium. Four with cancers of the body of the uterus show no evidence of recurrence from two to eleven years after discovery and after surgical removal. One with cancer of the vagina shows no recurrence four years after radical surgery. One with cancer of the ovary shows no recurrence four and one-half years after removal.

Eight of the seventeen volunteers with pelvic cancer have died of their cancers, as follows: one cancer of the cervix, one cancer of the body of the uterus, one cancer of the vagina, and 5 cancers of the ovary. The results of the treatment are summarized in Table IV.

TABLE IV. PRESENT STATE OF 17 VOLUNTEERS WITH PELVIC CANCER

		UTERINE CERVIX	UTERINE BODY	OVARY	VAGINA
Alive, no recurrence	9	3	4	1	1
Died of cancer	8	1	1	5	1

In addition to the 17 pelvic cancers, 986 benign lesions of the pelvic organs were found in the entire group of 1,319 volunteers throughout the fifteen-year period. These included 547 inflammatory lesions of the cervix generally believed to predispose to the development of cancer (Table V).

TABLE V. BENIGN LESIONS OF THE PELVIC ORGANS

Inflammatory lesions of the cervix		547
Other significant pathological conditions:		
Myomatous uterine tumors	216	
Mucous polyps of cervix	161	
Cystic tumors of ovary	41	
Leukoplakia of cervix	10	
Kraurosis vulvae	8	
Papillomas of cervix	2	
Tuberculous ulcer of vagina	1	439
Total		986

As a result of our recommendations, 247 of the inflammatory lesions of the cervix were eliminated by cauterization, conization, or excision. The examining physicians believe there is a direct relationship between these procedures and the small number of cancers of the cervix that have developed in the research group.

Breast Cancers

Beginning with January, 1942, the breasts of the volunteers were systematically examined. Some 11,203 breast examinations were made on the continuing group of 537 volunteers. Eleven breast cancers were found: 2 in single women, aged 51 and 81, respectively, 2 in married nulliparous women aged 55 and 60, 7 in married parous women from 42 to 76 years of age (Table VI).

TABLE VI. PERIODIC BREAST EXAMINATION RESEARCH JAN. 1, 1942, TO DEC. 31, 1952

Volunteers at beginning of research	545
Volunteers completing research	537
Number of breast examinations	11,203
Breast cancers found	11

All of the 11 breast cancers were first discovered by the volunteers themselves. One was discovered by a 76-year-old volunteer before examination of the breasts was included in the study. One was discovered by a 51-year-old WAC who, because of absence from Philadelphia, had not been able to visit the research clinic for twenty months. One was discovered by a 60-year-old volunteer, who, after a few visits, had decided she was too busy to come for examination. Ten years after her last visit she found a lump in her breast.

The other eight breast cancers were discovered by the volunteers themselves from three to six months after their breasts had been examined in the research clinic and no pathology found. The cancers varied in size from 0.5 cm. to 3 by 4 cm. in diameter.

In 6 of the 11 breast cancers, the axillary glands were not involved. Three of these volunteers are alive with no evidence of recurrence three, nine, and ten years after discovery and radical mastectomy. One died of coronary occlusion thirteen years after radical mastectomy with no evidence of recurrence. One is alive, with recurrence, seven and a half years after radical mastectomy.

In 5 of the 11 breast cancers, the axillary glands were involved. Three of these volunteers have died of cancer. Two are alive with no evidence of recurrence eleven and twelve years after radical mastectomy. One died of coronary occlusion three years after operation with no evidence of recurrence (Table VII).

TABLE VII. PRESENT STATE OF 11 PATIENTS WITH BREAST CANCER

Axillary glands not involved	6	
Alive, no recurrence, 3, 5, 10, and 11 years		4
Died, no recurrence, after 13 years		1
Alive, with recurrence, after 8 years		1
Axillary glands involved	5	
Alive, no recurrence, after 12 years		1
Died, no recurrence, after 3 years		1
Died of cancer, after 1, 3, and 3 years		3

Summary

As predicted by the late Dr. Ludvig Hektoen, who sponsored the research in the Committee on Clinical Research of the American Medical Association,

the chief value of this fifteen-year experiment was educational. As a result of examining hundreds of well women, the examining physicians became familiar with the appearance of the normal cervix and learned to appreciate the possible significance of deviations therefrom. The volunteers, as a result of the emphasis placed by the examining physicians on atypical uterine bleeding, vaginal discharge, and lumps in the breast, learned to appreciate the possible serious significance of these apparently trivial symptoms.

Speaking factually, the research led to the discovery of 17 pelvic cancers and 11 breast cancers, a total of 28 cancers in the continuing group of 537 volunteers over the fifteen-year period, or in 5 per cent of the entire group. It led to the discovery of 986 benign lesions of the pelvic organs, including 547 inflammatory lesions of the cervix generally believed to predispose to the development of cancer. It led to the elimination of 247 of these inflammatory lesions.

TABLE VIII. SUMMARY OF FINDINGS IN 537 CONTINUING VOLUNTEERS JAN. 1, 1938, TO DEC. 31, 1952

Cancers (Pelvic 17, breast 11)	28, or 5%
Lesions predisposing to cancer (Cervicitis, erosions, leukoplakia)	99, or 18%
Other significant pathology	303, or 56%
No pathology	138, or 25%

To the credit of the research study are 3 cancers of the uterine cervix with no recurrence fifteen and sixteen years after discovery and treatment by radium; four cancers of the uterine body with no recurrence from two to twelve years after discovery and surgical treatment; one cancer of the vagina with no recurrence four years after radical surgery, and one cancer of the ovary with no recurrence four and a half years after discovery and surgical treatment.

Six of the 11 patients with breast cancers are alive with no evidence of recurrence from three to twelve years after discovery and surgical treatment; 2 others died of coronary occlusion, with no recurrence of cancer, three and thirteen years after discovery and surgical treatment.

In spite of the discovery in the research clinic, radium and surgery failed to save the lives of one patient with cancer of the uterine cervix, one with cancer of the body of the uterus, one with cancer of the vagina, 5 with cancers of the ovary, and 4 with cancers of the breast.

Conclusions

This fifteen-year research has demonstrated the value of the periodic examination of the female pelvic organs and breasts of presumably well women. If the supply of physicians were unlimited, if time and money meant nothing to the lay public, such examinations could be recommended without reserve for all women 30 years of age and over. In the world as it is today, a more realistic approach to the problem becomes necessary.

This study and the experience of many other observers have demonstrated that the average woman can detect lumps in her breast quite as soon

as the average physician can. It seems, therefore, that the responsibility for breast cancer can safely be entrusted to the women themselves by means of educational programs.

The diagnosis of cancer of the body of the uterus is based upon symptoms which lead to diagnostic curettage. The continued education of women as to the possible serious significance of atypical uterine bleeding and discharge will probably lead to the early discovery of this disease quite as often as periodic examination would.

The fact that only one cancer of the ovary out of six was detected in a curable stage is discouraging and offers very little argument for periodic examination.

The four and a half year prolongation of life as a result of the discovery of one cancer of the vagina is offset by the early death of the other patient with cancer of the vagina.

Undoubtedly the greatest contributions made by the study were the discovery and consequent elimination of 247 lesions of the cervix generally believed to predispose to the development of cancer and the discovery of three cancers of the cervix of which there are no signs of recurrence fifteen and sixteen years after treatment by radium.

Cancer of the uterine cervix and lesions predisposing to its development occur most frequently in women 30 years of age and over who have borne children. On the basis of this research, we conclude that the death rate from cancer of the uterine cervix could be materially reduced if all such women were given a pelvic examination at least once a year. We recommend that this be adopted as a minimum standard for good medical practice.

Reference

1. Macfarlane, Catharine, Sturgis, Margaret C., and Fetterman, Faith S.: Am. J. Obst. & Gynec. **62**: 102, 1951.

136 South 16th Street (Dr. Macfarlane)

VAGINAL CYTOLOGY IN CANCER PATIENTS TREATED BY RADICAL HYSTERECTOMY*

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THE vaginal epithelium of women is sensitive to hormonal stimulation, and the exfoliated vaginal cells reflect the hormonal status. In the presence of adequate estrogenic stimulations, large numbers of cells desquamate from the superficial layers of the squamous epithelium as well as from the intermediate and occasionally from the deep layers, and the vaginal smears contain varying proportions of cornified cells; and in cases of very low estrogenic stimulation the epithelium becomes relatively atrophic and vaginal smears contain chiefly basal cells. Understanding this, one would expect to see vaginal smears with varying degrees of cornification in normal women during the childbearing age, and rather atrophic smears in women at the opposite extremes of the sexual life—prepubertal and postmenopausal—and in women who are castrated.

Many workers have shown, however, that vaginal smears in castrates as well as postmenopausal women, even many years after the cessation of menstruation, do not show uniform atrophic appearance. Salmon and Frank[1] found that only 40 per cent of castrates and postmenopausal women have atrophic smears; 30 per cent of them varied from atrophic to "follicular" and the remaining 30 per cent showed a definite "follicular" type. Papanicolaou and Shorr[2] concluded that some degree of estrogenic stimulation continues indefinitely after the menopause. Mack,[3] who felt that the glycogen index of vaginal epithelial cells was a more sensitive indication of estrogenic activity than the stained smears, found glycogen present in variable amounts in all age groups of women who have passed the menopause.

In 1933, Papanicolaou[4] wrote that not only was the estrogenic effect apparent, but that sexual periodicity was frequently observed in the vaginal smears of postmenopausal patients, some of them as late as ten years past the menopause. The sequence of periodic phases follows the same order as in normal young menstruating women. The "menstrual" phase in postmenopausal women is represented in the smear as an increase in leukocytes and deep-layer cells with microscopic bleeding. The "follicular" phase is represented by pronounced vaginal leukopenia. The "proliferative" and "premenstrual" phases are comparable to similar phases in the smears of normal young menstruating women. An irregular prolongation of these phases was evidenced in all cases and the longest sexual cycle observed lasted approximately

*Supported in part by funds from the National Cancer Institute, National Institutes of Health, United States Public Health Service.

five months. He also noted that these rhythmic changes seen in the vaginal smears of postmenopausal patients were related to their climacteric symptoms in that during the period of spontaneous change toward the "follicular" type of smears, the patients felt relieved of their symptoms.

Evidences as such indicate that in castrates and postmenopausal women the vaginal epithelium does not completely regress to an atrophic state and the vaginal smears still show varying degrees of estrogenic effect. One might expect that after the radical hysterectomy with bilateral salpingo-oophorectomy and pelvic lymphadenectomy, an operation designed primarily as a treatment of cancer of the cervix, the postoperative vaginal smears from these patients would be uniformly atrophic. The presentation here is a study of the vaginal smears from patients who suffered from carcinoma of the uterus or carcinoma of the vagina and who were treated by radical hysterectomy. The purpose of this investigation was to determine the general cellular composition of the vaginal smears of patients who had genital cancer, the pattern of cellular changes after the radical hysterectomy, and its relationship with the clinical progress of the patients.

The presentation has two parts: (1) the cellular pattern of the vaginal smears before and after the radical hysterectomy; and (2) correlation between the cellular pattern of vaginal smears and the prognosis of the patient.

Material and Method

The material is related to a previous report[5] on clinical aspects of 376 cases of radical hysterectomy with bilateral salpingo-oophorectomy and pelvic lymphadenectomy performed by gynecologists on the staff of the Vincent Memorial Hospital, the Massachusetts General Hospital, the Palmer Memorial Hospital and the Pondville Hospital (Massachusetts Department of Public Health) between 1939 and 1951. This report includes only the patients whose vaginal smears were read at the Vincent Memorial Hospital Cytology Laboratory, and so the group is limited to cases of the Vincent Memorial Hospital and the Massachusetts General Hospital.

All available smears were studied and recorded in regard to the relative amount of different cellular components. This was done by counting one hundred normal squamous epithelial cells in each smear with the respective percentages of cornified cells, intermediate cells, and basal cells obtained. The differential counts of the preoperative smears were charted on a graph and served as controls. Every postoperative follow-up smear of each patient was similarly counted and charted consecutively on the graph. Thus, there were three curves on the graph for each patient and the relative rise and fall of the three cell types during her course was readily seen. The number of smears from each patient varied from three to twenty-two. Graphs were not made in cases with less than three smears. In 154 patients, a sufficient number of smears was available. The maximum percentage of each cell type before and after radical hysterectomy was considered a significant value and used for comparison.

In 35 cases, the smears were counted previously, by more than one person. These differential counts have been compared with the ones used in this study. In 31 cases, the three curves of each of the duplicated graphs correspond very closely with less than 10 per cent differences. In 4 cases, the differences are more than 10 per cent but two of them show parallelism. This indicates that such differential counts on the three types of normal epithelial cells seen in the vaginal smears are reproducible.

Part I
Cellular Patterns of the Vaginal Smears Before and After the Radical Hysterectomy

There were 154 cases of radical hysterectomy with a sufficient number of vaginal smears available for this study (Table I). This number includes 104 cases of squamous carcinoma of the cervix, 12 cases of adenocarcinoma of the cervix, 11 cases of carcinoma of the cervical stump (squamous 9, adenocarcinoma 1, carcinoma in situ 1), 7 cases of carcinoma of the corpus, 2 cases of carcinoma of the vagina, 13 cases of squamous carcinoma in situ of the cervix, and 5 referred cases in which the diagnoses of malignancy were made in another hospital but at the radical hysterectomy no malignancy was demonstrated.

TABLE I. 154 CASES WITH VAGINAL SMEARS BEFORE AND AFTER RADICAL HYSTERECTOMY

Squamous carcinoma of cervix		104
Adenocarcinoma of cervix		12
Carcinoma of cervical stump		11
Squamous	9	
Adenocarcinoma	1	
Carcinoma in situ	1	
Carcinoma of corpus		7
Carcinoma of vagina		2
Carcinoma in situ of cervix		13
Referred cases		5
Total		154

The ages of these 154 patients varied from 17 to 75 years with the majority (102 cases) in the decades between 40 and 60 (Table II).

TABLE II. AGE DISTRIBUTION OF 154 PATIENTS

AGE	15-19	20-29	30-39	40-49	50-59	60-69	70-79
Number of patients	1	3	42	51	51	4	2

If this series is divided according to menopausal status, there were 90 patients in the premenopausal group and 64 patients in the postmenopausal group (Table III). Among the patients in the postmenopausal group, 47 had experienced the natural menopause from 2 to 25 years previously, 12 patients had a history of bilateral salpingo-oophorectomy from 1½ to 25 years previously, and ovarian tissue was not found at the radical hysterectomy. Five patients had had previous x-ray, resulting in postradiation amenorrhea of from 2 to 17 years' duration.

TABLE III. MENOPAUSAL STATUS OF 154 PATIENTS

Premenopausal		90
Postmenopausal		64
Natural menopause	47	
Previous bilateral salpingo-oophorectomy	12	
Post x-radiation menopause	5	

1. Vaginal Smears Before the Radical Hysterectomy.—

A common impression gained by many who used vaginal smears as one of the diagnostic aids is that patients who have cancer of the uterus often have relatively high estrogenic effect, as indicated by a well-cornified smear, even long after the menopause. An analysis of this aspect was done.

If an arbitrary level of 50 per cent was set as a dividing line, it was found that among the 154 patients, 47 of them had vaginal smears showing cornified cells occupying more than 50 per cent of the entire cell population, and 17 of them had smears showing more than 50 per cent basal cells before the operation (Table IV).

TABLE IV. VAGINAL SMEARS BEFORE RADICAL HYSTERECTOMY

		CORNIFIED CELLS ABOVE 50% LEVEL		BASAL CELLS ABOVE 50% LEVEL	
Premenopausal	90	35	(39%)	6	(7%)
Postmenopausal	64	12	(19%)	11	(17%)
Total	154	47	(31%)	17	(11%)

These cases were divided into premenopausal and postmenopausal groups (Figs. 1 and 2). In the postmenopausal group, only 17 per cent of the patients had predominately atrophic smears, the majority of them had moderate degrees of cornification (20 to 50 per cent cornified cells), and in 19 per cent of them the cornified cells were above the 50 per cent level.

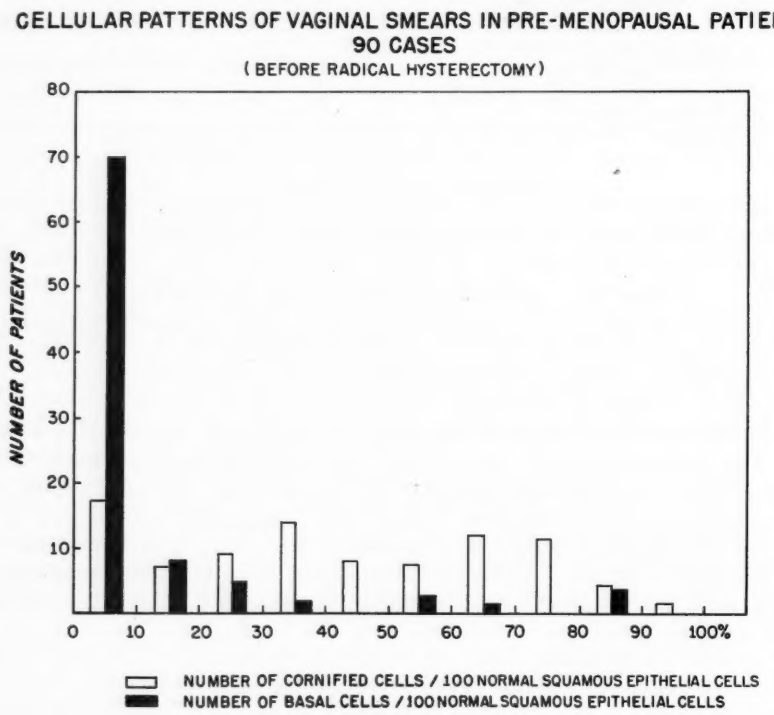

Fig. 1.

2. Vaginal Smears After the Radical Hysterectomy.—

Contrary to what one would expect, the vaginal smears after the radical hysterectomy did not show uniform atrophy (Table V). In only 27 per cent of the 154 cases did they become so. Twelve per cent of the patients still had cornified cells above the 50 per cent level, and the remaining major group exhibited varying degrees of cornification after the operation (Figs. 3 and 4).

Definite changes in the vaginal smears did occur, however, after the radical hysterectomy. When Table IV and Table V are compared, it is seen that

TABLE V. VAGINAL SMEARS AFTER RADICAL HYSTERECTOMY

		CORNIFIED CELLS ABOVE 50% LEVEL		BASAL CELLS ABOVE 50% LEVEL	
Premenopausal	90	14	(16%)	19	(21%)
Postmenopausal	64	4	(6%)	23	(36%)
Total	154	18	(12%)	42	(27%)

the number of patients with atrophic smears is now 27 per cent or more than twice the percentage seen before operation (11 per cent). The number of patients with well-cornified smears is now 12 per cent, or less than half the percentage present preoperatively (31 per cent). This change occurred in both the premenopausal and the postmenopausal groups. It seems to indicate that the radical hysterectomy caused certain degrees of changes in the vaginal smear pattern, and it affected both the patients in the premenopausal group and in the postmenopausal group alike.

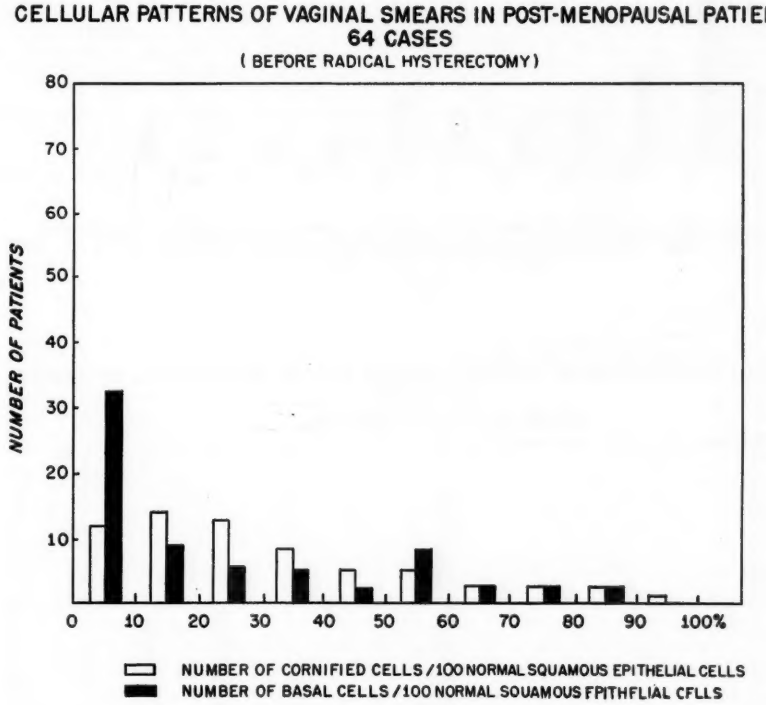

Fig. 2.

3. Relative Changes of Vaginal Smears in Individual Cases After the Radical Hysterectomy.—

An attempt was then made to compare the levels of each cell type in individual cases before and after the radical hysterectomy. Regardless of the initial levels of the cell count before the operation, an arbitrary figure of twenty per cent (either increase or decrease) was considered to be a change of apparent significance. Less than that, the changes were considered to be minor.

Among the 154 cases, 42 showed minor changes in either cell type after the operation, 24 showed a significant basal cell increase but no significant decrease in cornified cells, 30 showed a significant increase of basal cells as well as a decrease of cornified cells, and 38 showed a significant decrease of corni-

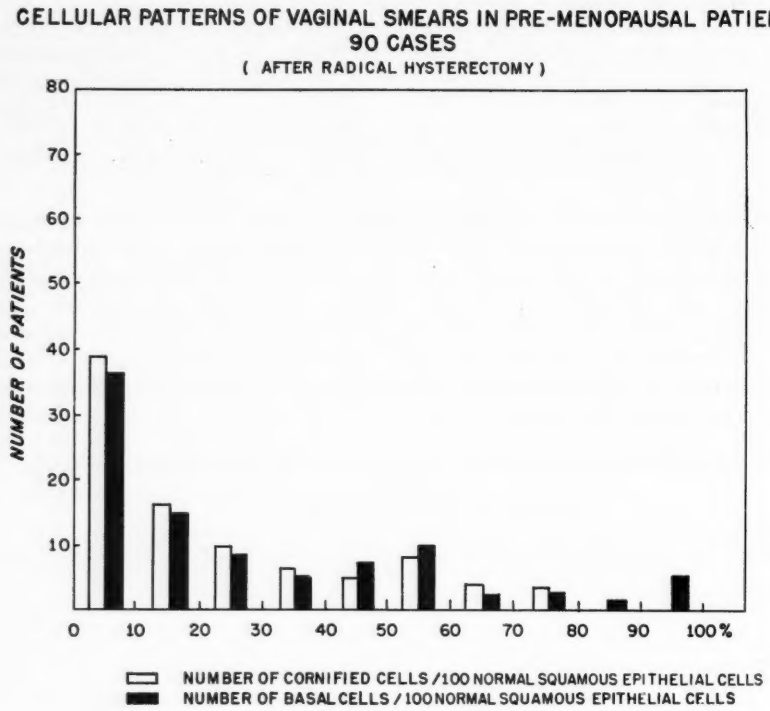
CELLULAR PATTERNS OF VAGINAL SMEARS IN PRE-MENOPAUSAL PATIENTS
90 CASES
(AFTER RADICAL HYSTERECTOMY)
NUMBER OF PATIENTS
80
70
60
50
40
30
20
10
0
10
20
30
40
50
60
70
80
90
100%
NUMBER OF CORNIFIED CELLS /100 NORMAL SQUAMOUS EPITHELIAL CELLS
NUMBER OF BASAL CELLS / 100 NORMAL SQUAMOUS EPITHELIAL CELLS

Fig. 3.

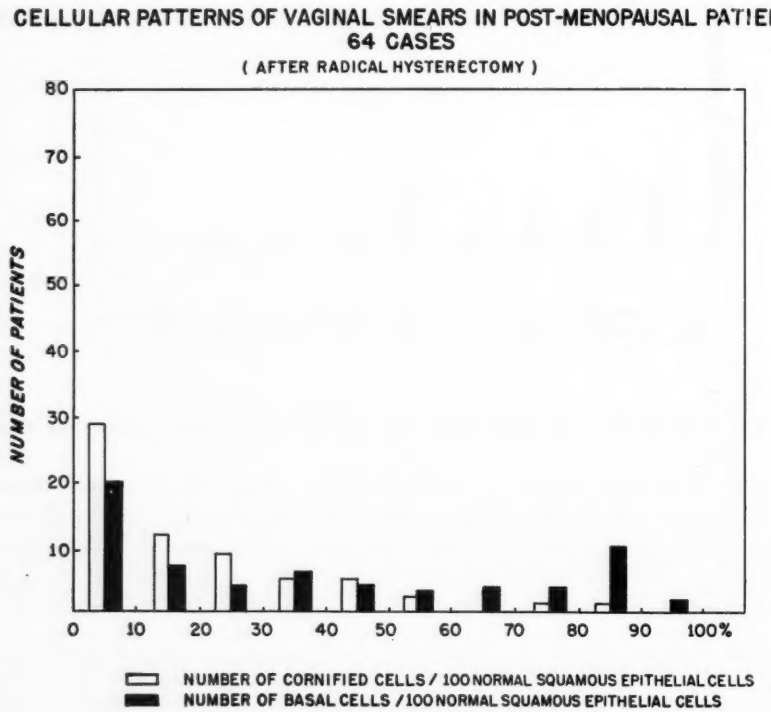
CELLULAR PATTERNS OF VAGINAL SMEARS IN POST-MENOPAUSAL PATIENTS
64 CASES
(AFTER RADICAL HYSTERECTOMY)
NUMBER OF PATIENTS
80
70
60
50
40
30
20
10
0
10
20
30
40
50
60
70
80
90
100%
NUMBER OF CORNIFIED CELLS / 100 NORMAL SQUAMOUS EPITHELIAL CELLS
NUMBER OF BASAL CELLS /100 NORMAL SQUAMOUS EPITHELIAL CELLS

Fig. 4.

TABLE VI. CELLULAR CHANGES IN VAGINAL SMEARS AFTER RADICAL HYSTERECTOMY

	PREMENOPAUSAL 90 PATIENTS		POSTMENOPAUSAL 64 PATIENTS		TOTAL 154 PATIENTS	
	NO.	%	NO.	%	NO.	%
A change of less than 20 per cent of either cell type	24	27	18	28	42	27
A change of more than 20 per cent:						
Basal cells increase	12	13	12	19		
Basal cells increase and cornified cells decrease	17	19	13	20		
Cornified cells increase	28	31	10	16		
	57	63	35	55	92	60
Cornified cells increase	4	5	5	8		
Cornified cells increase and basal cells decrease	2	2	2	3		
Basal cells decrease	3	3	4	6		
	9	10	11	17	20	13

fied cells only. On the other hand, 9 patients had actually a significant increase of cornified cells after the operation. Seven patients had a significant decrease in basal cells and 4 patients had both (Table VI).

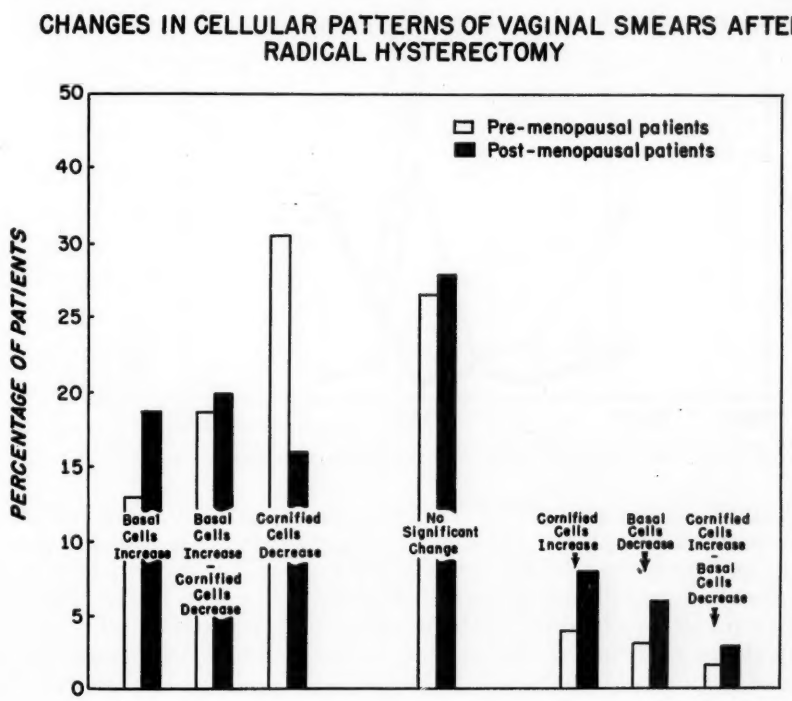

Fig. 5.

In substance, 27 per cent of the patients showed very minor changes in the cellular composition of the vaginal smears after the radical hysterectomy, 60 per cent of the patients showed an apparent change toward what one would expect after the radical operation, and in the remaining 13 per cent of the patients, the changes which occurred in the vaginal smears were those which are ordinarily interpreted as of increasing estrogenic effect.

The proportions of patients without any significant changes in the smears after the radical hysterectomy were almost identical in the premenopausal and postmenopausal groups. It seemed, however, that a few more patients in the postmenopausal group (17 per cent) than in the premenopausal group (10 per cent) had the tendency to show a rebound estrogenic effect after the radical hysterectomy (Fig. 5).

Part II
Cellular Patterns of Vaginal Smears and Prognosis of the Patients

Among the total number of 154, 58 patients with invasive carcinoma of the uterus had the radical hysterectomy five or more years ago and are living and well. (Carcinoma in situ and referred cases are excluded.) There were also 39 patients who had the radical hysterectomy from 2 to 5 years ago who are dead or have had recurrence. The graphs of these 97 patients were compared and studied.

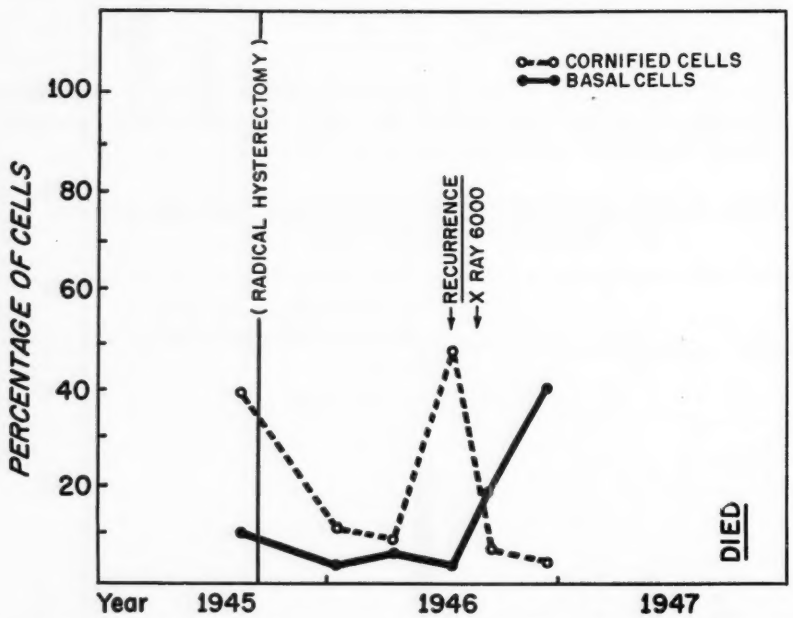

Fig. 6.—F. W., No. 496156, aged 36 years. Squamous carcinoma of the cervix, Stage I.

One common observation obtained from the graphs of these patients was that the levels of different cell constituents fluctuated. An attempt was made to correlate the fluctuating levels of cornified cells in the postoperative smears with the clinical course of the patients. In 5 patients who succumbed to their disease, a sharp rise of cornified cells occurred either preceding or at the time of the clinical recognition of recurrence. Fig. 6 shows the graph of one of these. In the majority of patients, however, an apparent correlation did not exist.

Though the percentage of cornified cells did not appear to be significant in prognosis, the number of basal cells before and after the radical hysterectomy did seem of importance in this regard.

1. Basal Cells in Preoperative Smear and Prognosis.—

The graphs of these 97 patients were examined as to the basal cell counts in the initial vaginal smears before the radical hysterectomy (Table VII). It

TABLE VII. PREOPERATIVE BASAL CELLS AND PROGNOSIS*

BASAL CELLS IN PREOPERATIVE SMEAR	NUMBER OF PATIENTS	ALIVE AND WELL*
Below 50 per cent	85	54 (64%)
Above 51 per cent	12	4 (33%)
(Above 60 per cent)	(6)	0

*These figures do not indicate the five-year salvage rate, as they include not only patients living and well five years but also patients operated upon more recently who have developed recurrence or died.

is seen that 85 patients had preoperative basal counts below 50 per cent and 12 patients had them above the 51 per cent level. Among the 85 patients whose preoperative basal cells were below 50 per cent, 54 (64 per cent) are alive and well. Among the 12 patients with rather atrophic smears before the radical hysterectomy, 4 (33 per cent) are alive and well. Moreover, 6 of these 12 patients had preoperative basal counts above 60 per cent; all are now dead or have recurrence. It indicates that in those patients who had a high level of basal cells in the preoperative vaginal smear, the prognosis after the radical hysterectomy is poor. Fig. 7 shows the graph of one of them.

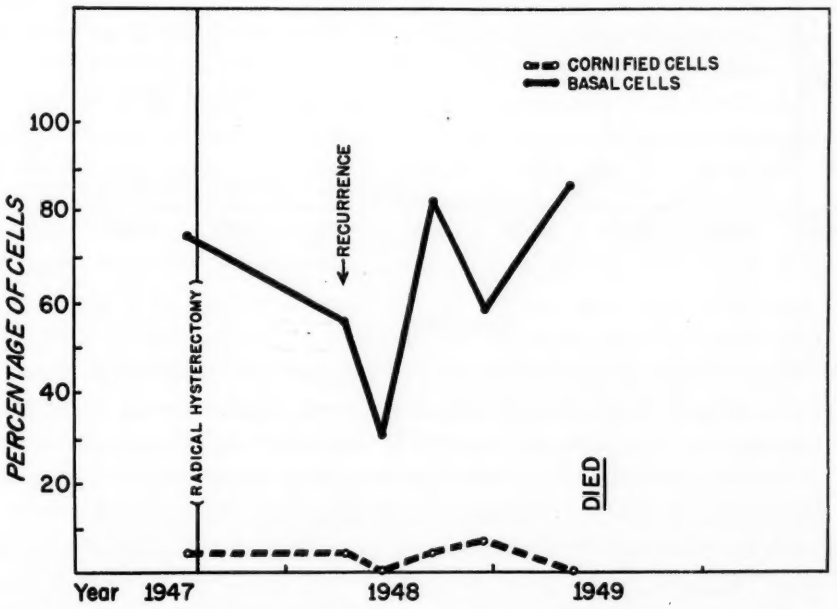

Fig. 7.—M. D., No. 583439, aged 57 years. Squamous carcinoma of the cervix, Stage I.

2. Basal Cells in Postoperative Smears and Prognosis.—

Regardless of the actual percentages of the basal cells in the smears, if a comparison was made between the preoperative and the postoperative levels, it was found that 44 patients had a 20 per cent increase of basal cells after the radical hysterectomy and 53 patients did not have such an increase (Table VIII).

Among the 44 patients in whom radical hysterectomy brought about a substantial increase in basal cells, 34 (80 per cent) are alive and well. Among the 53 patients in whom the operation failed to bring such an increase of basal cells, 24 (45 per cent) are alive and well. It showed that a significant increase of basal cells after the radical hysterectomy was one of the indications that the prognosis after the radical hysterectomy would be good. Fig. 8 shows the graph of one of these patients.

TABLE VIII. POSTOPERATIVE BASAL CELLS AND PROGNOSIS*

BASAL CELLS IN POSTOPERATIVE SMEAR	NUMBER OF PATIENTS	ALIVE AND WELL*
With 20 per cent increase, or more	44	34 (80%)
Without 20 per cent increase	53	24 (45%)

*These figures do not indicate the five-year salvage rate, as they include not only patients living and well five years but also patients operated upon more recently who have developed recurrence or died.

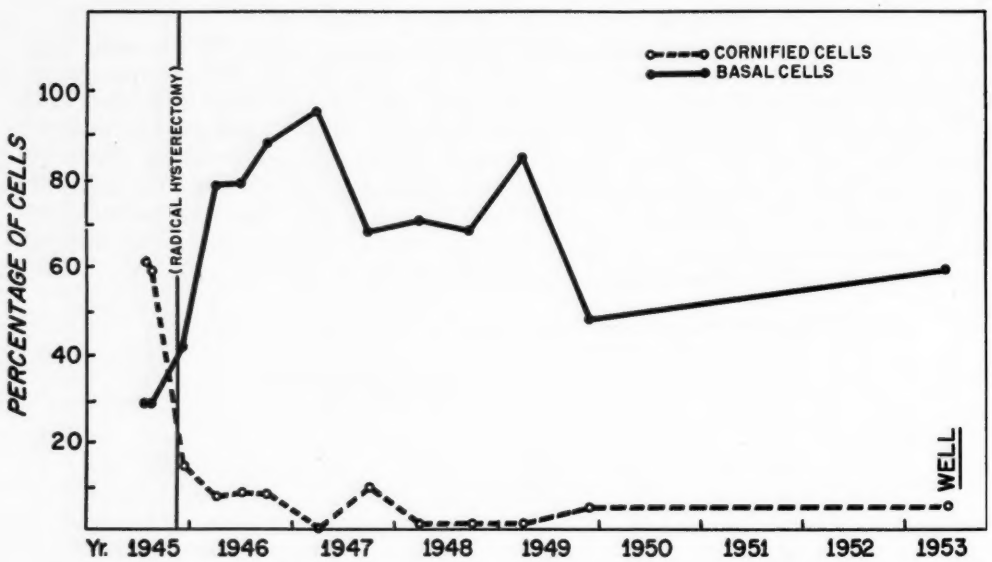

Fig. 8.—A. A., No. 412939, aged 33 years. Squamous carcinoma of the cervix, Stage I.

Comment

The failure of vaginal epithelium to become uniformly atrophic following the menopause, spontaneous or induced, may be explained by an extragenital source of estrogens. The adrenal cortex is regarded as the source of these materials. Woolley, Fekete, and Little[6] have shown in brown mice that after gonadectomy in either male or female, hyperplasia of the adrenal cortex occurred which was followed by changes characteristic of feminization in these animals. The biological action of desoxycorticosterone in castrated rhesus monkeys was demonstrated by Speert[7] in producing growth of the mammary gland, uterine bleeding, coloring of sex skin, etc. In human beings, according to Salmon,[8] typical estrogenic effects were produced in the vaginal smears of postmenopausal women with desoxycorticosterone acetate. Among the 64 postmenopausal patients in this study group, only 17 per cent had relatively atrophic smears. This is a proportion less than that reported in the recent literature on the studies of postmenopausal vaginal smears.[9, 10] It suggests that the nonatrophy of the genital tract in postmenopausal women is more prevalent in patients who have cancer. Contrary to what one would expect, after the radical hysterectomy, the vaginal smears of these patients did not show uniform atrophy. Only 27 per cent of the 154 patients had relatively atrophic smears after the operation.

The radical hysterectomy seemed, however, to have a definite influence on the hormonal status of some patients since the number of patients with well-cornified smears and the relatively atrophic smears were reversed before (31 per cent and 11 per cent, respectively) and after (12 per cent and 27 per cent, respectively) the operation. Furthermore, this is true for both the premenopausal and the postmenopausal groups, and it indicated that the radical hysterectomy affected both groups similarly in producing atrophic smears. A larger number of premenopausal than postmenopausal patients, however, had well-cornified smears before the operation. Therefore, a higher proportion of premenopausal patients maintained their cornified smears after the operation. It suggested that the cornified smears of only a certain percentage of patients could be changed to atrophic smears by the radical hysterectomy. Both the premenopausal and postmenopausal groups were affected to a similar degree.

The amazingly close percentages of patients in the premenopausal and the postmenopausal groups who did not show any significant changes in the vaginal smears after the operation (27 per cent and 28 per cent, respectively) suggested again that there was also an equal quota of patients in each group on whose hormonal status the radical hysterectomy could exert no influence.

A correlation was sought between the general cellular patterns of vaginal smears and the clinical progress of the patients. The data suggested that in only occasional cases a sudden rise of cornified cells in the smear during the follow-up period correlated well with the recurrence. Generally, the basal cells in the smears before and after the radical hysterectomy were of more importance.

Patients who had carcinoma of the uterus and who had very low estrogenic effect as represented by relatively atrophic smears before the treatment did very poorly after the radical hysterectomy. This was indicated by 12 patients whose preoperative smears contained more than 50 per cent basal cells and of these only 4 patients lived. Furthermore, none of the 6 patients survived whose preoperative smear contained more than 60 per cent basal cells.

Patients who had a pronounced change in estrogenic effect following the radical hysterectomy, as reflected by an increase in basal cells in the postoperative smears were more often associated with a favorable clinical course than the patients without such a change. This was indicated in almost half of the series, 44 of 97 patients, who showed an increase of more than 20 per cent of the basal cells in the postoperative smears, with a five-year survival rate of 80 per cent.

It seems, therefore, that two points of information are obtainable from vaginal cytologic patterns which may be of help in indicating the prognosis of the patients with cancer of the uterus treated by radical hysterectomy: (1) if the initial vaginal smears before the operation contain high levels of basal cells (above 50 per cent) a poor prognosis is suggested, and (2) if a significant increase of basal cells (more than 20 per cent) in the vaginal smears occurs after the radical hysterectomy, a favorable prognosis is to be expected.

In the first regard, Graham and Graham[11] have shown that patients with carcinoma of the cervix would respond well to radiotherapy if their initial

vaginal smears before the treatment show the "Sensitization Response." This specific gauging index of radiosensitivity is found chiefly in the basal cells. This study suggests that patients with relatively atrophic smears have a less favorable prognosis than those with moderately cornified smears when treated surgically. It may be that this is the group of patients in whom surgical treatment is not indicated and in whom radiation could achieve a better salvage. In the second regard, this study seems to agree with the observation of many others that a change of the environmental or hormonal status of the host interferes with the prosperity of the cancer growth.

Summary

1. This is a study of cellular patterns of vaginal smears from patients with genital cancer who were treated with radical hysterectomy, bilateral salpingo-oophorectomy, and pelvic lymphadenectomy. The material came from patients whose vaginal smears were submitted to the Vincent Memorial Hospital Cytology Laboratory.

2. The relative amount of different cellular constituents in a smear was obtained by counting one hundred normal squamous epithelial cells with the relative percentage of cornified, intermediate, and basal cells. The differential counts of the preoperative and the postoperative smears of a patient were charted consecutively on a graph, and the relative rise and fall of each cell type during her course were readily seen.

3. One hundred fifty-four patients had sufficient numbers of vaginal smears for the study of cellular patterns, before and after the radical hysterectomy. Ninety patients were premenopausal and 64 were postmenopausal. In the postmenopausal group, the majority had moderate to marked cornification of the smears, and only 17 per cent of the patients had atrophic smears before the operation. Contrary to what one would expect, vaginal smears after the radical hysterectomy did not show uniform atrophy. The smears of only 27 per cent of the 154 patients became so, and 12 per cent of the patients still had well-cornified smears. Radical hysterectomy, however, seemed to have a definite influence on the hormonal status of these patients, since the proportion of well-cornified smears and the relatively atrophic smears were reversed before and after the operation. The data suggest that there are only a certain number of patients whose cornified smears could be changed to atrophic by radical hysterectomy, and both the premenopausal and the postmenopausal groups were affected to a similar degree. It also suggests that there are patients in both groups on whose hormonal status the radical hysterectomy exerts no influence.

4. There were 97 patients whose graphs were compared as to the cellular pattern of vaginal smears and the prognosis. The basal cells in the smears before and after the radical hysterectomy seemed to be of prognostic importance. Patients with cancer of the uterus who had atrophic smears before the treatment responded poorly to radical hysterectomy. The majority of the patients

whose preoperative smears contained moderate cornification and whose postoperative smears showed a subsequent increase of basal cells usually had a favorable prognosis. The possible explanation of the correlation was discussed.

I wish to express my sincere appreciation to Dr. J. B. Graham and Mrs. R. M. Graham for their advice and help in reading the manuscript.

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PROPHYLAXIS AND PALLIATION OF MALIGNANT EFFUSIONS WITH RADIOACTIVE COLLOIDAL GOLD

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IN THE past few years, radioactive colloidal gold has come into use in the treatment of ascites and pleural effusions resulting from metastatic neoplasms.[1-4] It has been suggested that radioactive gold may be of some value as a prophylactic measure in selected cases.[1] This is a preliminary report and evaluation of the clinical results of the prophylactic and palliative use of radiogold in 34 cases treated from January, 1952, to December, 1953. It does not include 35 cases treated since December, 1953. Other purposes of this report are to clarify the indications and limitations of the uses of radiogold and to describe our technique and experience.

The purpose of gold administration is to deliver ionizing radiation directly to the serous tissue implants with a minimum of radiation to normal tissue or to the hemopoietic and gastrointestinal systems. Gold (Aurcoloid-198*) is suitable for this purpose because of its physical, chemical, and colloidal properties. The physical half life is 2.7 days. It has beta radiation with a maximum range in water of 3.8 mm.; and gamma radiation of 0.41 mev. The colloidal particle size is approximately 0.003 to 0.007 microns.[5] The gold is chemically inert.

When the radioactive colloidal gold, distributed in a suitable amount of isotonic saline solution, is instilled into the peritoneal or pleural cavities, the gold "plates" out on the serous surface by a process of adsorption and phagocytosis so that the radioactive material disappears from the free fluid in the cavity. Goldie and Hahn[6] have shown that the macrophages present in the ascitic fluid carry gold particles to the walls of the cavity. This concentration on the tissue has been demonstrated by radioassay and autoradiographic studies,[7] with 50 per cent of the radioactivity being removed from the free fluid in from 24 to 48 hours.[8] By these mechanisms the radioactive material is placed in intimate contact with the malignant cells and delivers radiation to them.

The basic problem of dosage is to administer sufficient radiation to produce the desired therapeutic effect without inducing serious damage to normal tissue or severe systemic reactions. Doses as high as 225 millicuries in the peritoneal cavity have been tolerated without complication and doses as low as 100 millicuries have produced palliation. The average dose used at present is approximately 160 millicuries to the peritoneal cavity which will deliver an estimated 4,800 r equivalent physical of beta radiation to the peritoneal serous surface area in 11 days.[9] The average pleural dose is 60 millicuries.

*Radioactive colloidal gold, Au^{198}, was supplied by Abbott Laboratories, North Chicago, Ill.

Indications

One of the frequent complications of metastatic malignant disease, particularly with primary tumors of the breast or ovary, is the recurrent accumulation of fluid, either in the peritoneal or pleural spaces or in both. The repeated removal of the fluid is of only short benefit to the patient and at the same time depletes the body of essential fluids and protein. Either or both cavities may respond to radiogold treatment. Although the transport of colloidal material from one serous cavity to the other has been demonstrated,[10] the amount transferred is insufficient to produce a therapeutic effect in the untreated cavity.

The ascites or pleural effusion should be recognized and treated early in the course of the patient's illness. In one case of primary ovarian carcinoma with ascites with a history of 125 taps of approximately 3 gallons each over a period of 3 years, two administrations of gold (190 millicuries and 192 millicuries, 14 weeks apart) failed to control the recurring ascites. This may indicate that certain changes may take place in the serous cavity after numerous aspirations of fluid over a long period of time, so that the mechanism of fluid production becomes irreversible. This particular case also failed to respond to deep x-ray therapy given prior to the gold therapy.

The exact mechanism by which the fluid is produced in metastatic malignant disease of serous cavities has not been satisfactorily explained. Goldie and Hahn[6] have shown that the introduction of radioactive colloidal gold into the serous cavities of mice will inhibit the formation of fluid and destroy some of the malignant cells. Andrews and associates[8] have observed a comparable effect in human beings, that is, a disappearance of free tumor cells from fluids aspirated after the patients were treated with radiogold. This would indicate that a biologic change can be induced so that the formation of fluid in the serous cavity is decreased or completely inhibited after a single intracavitary injection of radiogold.

Cases considered suitable for this type of treatment may be classified in two groups; (1) palliative and (2) prophylactic. The primary purpose of the treatment in the palliative group is to inhibit the reaccumulation of fluid in the chest or abdomen where the fluid is already present as a complication of malignancy. These cases ordinarily require repeated removal of the fluid in order to relieve the patient of pressure symptoms. Relief from repeated fluid withdrawal is in itself of significant benefit to the cancer patient.

Beginning in January, 1952, cases in which a malignancy is most likely to produce ascites were selected and treated with gold before any appreciable amount of fluid had formed or any taps were required. This group consisted of 10 patients with an established diagnosis of carcinoma of the ovary. During surgery, the primary tumor was entirely or partially removed. The findings at the time of surgery indicated in all cases that there was residual malignancy such as peritoneal implants. It was felt that the formation of ascites as a later complication was highly probable in each of the cases be-

cause of implants already present or the possibility of implantation due to rupture of the cyst during surgical extirpation. The purpose of the gold treatment in this group of cases is to decrease the possibility of implantation of malignant cells by the destruction of the free-floating cells at a time when they are most vulnerable to the short-range beta radiation.

In considering a patient for gold treatment, a careful evaluation of the patient's general condition, blood count, the presence or absence of large intra-abdominal masses, and the rate of fluid accumulation is made. In properly selected cases, radiogold can relieve the distressing pressure symptoms resulting from massive accumulation of pleural or ascitic fluid. Haas and co-workers[11] have stated recently, "The term 'hopeless' should not be applied to any cancer patient until all known therapeutic measures have been attempted, or the patient is in a terminal status. 'Hopeless' should not be used just because one particular method of treatment offers no chance of cure or good palliation."

The over-all evaluation of the intracavitary radiogold treatment is made difficult when it is given in terminal cases. The general condition of the patient should warrant the use of this method as a palliative or prophylactic rather than as a heroic measure.

Some investigators have injected radiogold directly into tumor masses which are relatively accessible, for example, intraparametrially[12] for carcinoma of the cervix, or directly into prostatic tumors.[13]

Administration Apparatus and Techniques

The concentrated gold colloid, 6 to 10 c.c. in a sealed sterile bacterin vial, is brought to the point of delivery in a heavy lead shield affording 3 cm. of lead in all directions and a 3 cm. retaining wall to contain any spills due to faulty puncturing of the vial. Two No. 15 needles are inserted into the vial through the rubber seal, one deep in the liquid, the other only to the air space above. A 200 c.c. intravenous infusion apparatus is connected to the shallow needle and the isotonic saline solution flushes the colloidal material through the deep needle into the cavity. Approximately 50 c.c. of saline solution is usually sufficient to remove all of the characteristic red color from the vial, additional saline being added to ensure flushing of the apparatus and to provide adequate volume and dilution for the dose. The needle-to-rubber seal has been tested to pressures of 250 mm. of mercury.

For intraperitoneal administration, entry to the cavity may be made by means of a small laparotomy into which a No. 14 French catheter is placed. The tissues are closed in order and an untied purse-string suture around the catheter makes it possible to close the opening tightly immediately after withdrawal of the catheter. No gold is delivered until all surgical procedures are completed to minimize the time of exposure. When gold is administered following a paracentesis, the trochar is left in place after withdrawal of ascitic fluid, a No. 10 French catheter is threaded through the trochar into the cavity, the trochar is withdrawn, and the gold delivery apparatus flushes gold and saline through the catheter into the cavity.

Gold is administered to the chest only following a thoracentesis to ensure that the needle is properly located in the pleural space. The needle and

regular three-way thoracentesis stopcock are left in place after aspiration of pleural fluid. The delivery apparatus is connected to the three-way stopcock, the gold and saline delivered, and the needle withdrawn.

All gold administrations are carried out with the proper aseptic technique.

Radiation Hazard to Personnel Administering Gold

The radiation hazard to all personnel concerned must be carefully evaluated and protective measures taken to ensure that the dose received remains within the permissible 300 milliroentgens per week. The most effective means of protection are distance, speed of operation, and shielding. Suitable instruments for measuring radiation levels and dose received must be employed. Our experience has been with the handling of approximately 300 millicuries per week distributed in several hospitals, so that one hospital rarely has more than two cases during any one month. If larger doses are given, or if more varied and frequent procedures are instituted, additional radiation precautions and more detailed monitoring will be required.[15, 16]

Our experience with the administration technique described indicates that the gamma dose received by personnel administering the gold is well within the permissible level of 300 milliroentgens per week. Because of the speed and simplicity of the procedures of preparation and delivery, doses to personnel are rarely as high as 50 milliroentgens and are usually near 20 milliroentgens for one administration. Hospital personnel and surgeons encounter radiation even less frequently than our laboratory personnel, and their exposure can be considered negligible. Doses received by the surgeon and his assistants, however, are measured and reported to the surgeon.

Personnel who administer the radioactive gold wear pocket ionization chambers and film badges throughout all phases of the preparation and delivery of the gold to the patient. In any phase of the work in which the gold leaves the original container, rubber gloves and surgical gowns are worn to protect against spattering or contamination which may cause skin burns. All radiation fields are monitored by survey instruments before they are entered. Pocket chambers are issued to the surgeon and his assistant to cover their phase of the work and practically all surgical techniques are completed before any gold is delivered from its shielded container to minimize exposure time.

In addition to monitoring the gamma dose received by personnel, the hands, faces, and garments of these personnel are also surveyed for beta radiation after the patient has been removed from the operating room.

Radiation Hazard to Nursing Personnel

The radiation hazard to nursing personnel in the postoperative care of the patient who has received a treatment of radioactive gold of approximately 150 millicuries or less is usually overestimated. Survey of such patients with Geiger-Mueller instruments previously calibrated against a radium standard show on the average 20 milliroentgens per hour at a distance of 3 feet from the abdomen and 10 milliroentgens per hour at 5 feet. An ionization-chamber type of instrument shows about 1,200 milliroentgens per hour at the surface of the abdomen, and the radiation may be as high as 2 r per hour.[17] These values represent gamma radiation immediately after the administration of the gold. The radiation, of course, decays exponentially with a half life of 2.7 days.

On the basis of these levels of radiation, it is extremely improbable that any nursing personnel would receive an exposure of anywhere near the 300 milliroentgen permissible weekly dose in the normal course of their duties.

TABLE I. SUMMARY OF CASES TREATED PROPHYLACTICALLY

CASE SEX AGE	DIAGNOSIS	OPERATION AND FINDINGS	INTRAPERITONEAL DOSE	RESULTS	
				ASCITES	TIME
No. 546 Female 63 years	Papillary cyst-adenocarcinoma of ovary	1943—Subtotal emergency hysterectomy and bilateral salpingo-oophorectomy 1952—Removal of cervical stump with tumor mass and fundus of bladder	130 mc.	None	Patient died in 19 months
No. 689 Female 74 years	Adenocarcinoma of ovary	Primary tumor adherent, partially removed	187.5 mc.	None	Patient alive 14 months
No. 693 Female 52 years	Papillary adenocarcinoma ovary	Right oophorectomy and excision of omental cake. Capsule perforated. Implants on pelvis and peritoneum	194 mc.	None	Patient died in 2 months
No. 699 Female 63 years	Hemangioendothelial sarcoma (primary in omentum)	1949—Supracervical hysterectomy, bilateral salpingo-oophorectomy (90%) removed. Metastases to ovary and uterus 1952—Laparotomy; tumor inoperable	237 mc.	None	Patient died in 11 months
No. 749 Female 28 years	Granulosa-cell carcinoma of ovary	Subtotal hysterectomy, left salpingo-oophorectomy. Right ovary and omentum adherent. Generalized abdominal metastases (small nodules)	200 mc.	None	Patient died in 5 months
No. 771 Female 48 years	Adenocarcinoma of ovary	Laparotomy, left oophorectomy with peritoneal implants	180 mc.	None	Patient died in 5½ months
No. 789 Female 50 years	Papilliferous cystadenocarcinoma of ovary	1952—Total hysterectomy, bilateral salpingo-oophorectomy. Tumor removed. Left ovary ruptured and exuded tissue typical of carcinoma	175 mc.	None	Patient alive 11 months
No. 818 Female 49 years	Adenocarcinoma of ovary	1952—Inoperable widespread metastases. Biopsy taken	171 mc.	None	Patient died in 16 months
No. 1040 Female 46 years	Cystadenocarcinoma of ovary	1953—Laparotomy, fluid removed, bilateral oophorectomy	220 mc.	None	Patient alive 6 months
No. 1187 Female 46 years	Adenocarcinoma right breast; adenocarcinoma of ovary	Right radical mastectomy. Partial omentectomy. Malignant involvement of omentum. Carcinomatous (small) implants on ovaries	111 mc.	None	Patient alive 5 months

In our earlier cases, we issued film badges to nursing personnel who might come in contact with the patient. These were developed and evaluated by comparison with badge standards prepared in our laboratory by exposing similar films to known values of the gamma radiation from gold measured by Victoreen pocket chambers, or to known values of gamma radiation from a radium standard. The comparison was made on the basis of film blackening measured with a photodensitometer. Dosages were always low, usually under 50 milliroentgens for the first three days. In one case, where a relative of the patient remained at the bedside for most of the first day, the dose measured was approximately 150 milliroentgens.

On the basis of this experience, the detailed monitoring of nursing personnel subjected to infrequent exposure has been discontinued. Our instructions are that the patient should be treated as one with a radium implant for the first three days as far as radiation is concerned, and that a different nurse give the patient her bath each day for the first three days. With other patients in the room, beds should be at least nine feet apart.

Side Reactions and Precautions

One of the possible side effects associated with any type of radiation therapy is the reaction of the hematopoietic system. Andrews and co-workers[8] report mild radiation damage to the bone marrow evidenced by lymphopenia followed by mild depression of the granulocytes and thrombocytes. With an extremely large total dose a severe leukopenia may develop. These effects may be due to the gamma irradiation of the liver and spleen and the beta irradiation of the bone marrow, liver, and spleen, due to gold absorbed by these tissues following intracavitary administration. Botsford and collaborators[18] reported 4 cases of aplastic anemia following therapy with radioactive gold. Only one of these, however, was treated by intraperitoneal injection; 3 were treated by direct injection into tumor masses. Seaman and his associates[19] reported 74 cases treated by intracavitary administration with only mild leukopenia. In our series of cases, the only significant hematologic complication was the development in one case of an acute lymphatic leukemia five months after therapy. It is doubtful that this was related to the gold treatment.

Less serious side effects occur relatively frequently in the form of nausea, vomiting, diarrhea, anorexia, presumably due to irradiation of the gastrointestinal tract. In this series of cases, most of those patients who had the administration carried out under general anesthesia developed these gastrointestinal symptoms; however, those patients who had the procedure carried out under local anesthesia developed these symptoms only slightly. The side effects on the gastrointestinal tract were easily controlled. Only one patient in our series developed the gastrointestinal symptoms to any great extent and this patient had been found to be extremely radiosensitive to x-ray therapy also.

In the administration technique described, the gold is diluted to a concentration of 1 millicurie per cubic centimeter or less. This precaution, together with motion of the patient to ensure distribution throughout the cavity, minimizes the possibility of radiation necrosis due to loculation which might deliver excessive radiation to a small area. Careful closure and cleansing of the site of administration prevent beta burns of the skin which might occur if some of the colloid were to dry on the skin.

In planning the treatment of serous-cavity metastases with fluid, the question of supplementing radiogold treatment with deep x-ray therapy has been raised frequently. In planning such therapy, the time interval after the gold therapy, the tissue dose administered by the gold, and the condition of the blood elements should be carefully considered.

TABLE II. SUMMARY OF CASES TREATED THERAPEUTICALLY (INTRAPERITONEAL AND INTRAPLEURAL ADMINISTRATION)

A. Patients Living, December, 1953.—		
1. Number of patients living		10
2. Number not requiring repeated taps		7
3. Length of time since treatment		
	12 months	2
	9 months	2
	6 months	2
	3 months	1
	2 months	2
	1 month	1
B. Patients Who Died Prior to December, 1953.—		
1. Number of patients		14
2. Number not requiring repeated taps		14
3. Number surviving		
	1 month	13
	3 months	6
	9 months	1

Summary of Cases

The 34 cases treated are summarized in Tables I and II. Ten cases are classified as prophylactic and 24 are classified as therapeutic. Table I includes the group classified as prophylactic and is comprised of those cases in which the gold was administered intraperitoneally, before fluid formation, when the diagnosis and surgical findings indicated a malignancy with which ascites is a frequent complication. The diagnosis in every case was made by surgical exploration and biopsy of the primary tumor. None of the patients treated prophylactically developed ascites throughout their life span in this study. Six of the 10 lived six months or longer after the procedure and 5 are living at the time of this report.

Table II is made up of those cases in which the gold was given therapeutically, either intraperitoneally or intrapleurally. If fluid did not recur in the cavity, or if only one tap was required during the survival span of the patient, the patient was considered palliated. Table II shows that of the 24 patients treated therapeutically, 7 survived 6 months or more without requiring repeated taps. Only 5 of the 25 required a single additional aspiration before complete cessation of fluid formation.

Conclusions

1. A preliminary report is presented of our experience using radioactive colloidal gold as a prophylactic or therapeutic measure for patients with an accumulation of chest or abdominal fluid in association with malignant tumors. Although 69 doses have been administered to date, this report includes only the 34 cases treated from January, 1952, to December, 1953.

2. The indications and contraindications for the intracavitary use of gold are described.

3. The procedures of administration and related radiation problems are discussed.

4. Side reactions to radiogold therapy and precautionary measures are described.

5. A total of 10 patients were treated prophylactically. Of these, none developed ascites and 6 survived six months or longer. These data are presented with no attempt at a conclusion as to the effectiveness of the treatment.

6. A total of 24 patients were treated therapeutically. Of these 8 survived six months or longer and 7 were palliated, that is, did not require repeated fluid aspirations.

7. In the group of patients in whom the gold produced the desired effect, that is, inhibited the reaccumulation of fluid in the abdomen or chest, the general condition of the patient also showed considerable improvement.

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VAGINAL HYSTERECTOMY*

Operative Technique

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VAGINAL hysterectomy with repair of defective pelvic supporting structures when present is one of the most useful of all gynecological operations. Its increasing popularity is well attested by the large series being reported in the current literature.[1-6] Particularly impressive are the greater safety and comfort of the patient with a high percentage of symptomatic relief as compared to results obtained with abdominal hysterectomy or with one of the various pelvic plastic procedures without removal of the uterus.[7-10] Actually, vaginal and abdominal hysterectomy should not be competitive operations as there is a definite place for each and usually clear-cut indications or contraindications. The merits of the vaginal approach will not be discussed here; suffice it to say that with increasing familiarity with the operative technique we will find more and more patients to whom this procedure is applicable.

Preoperative Work-up

A meticulous history is taken, followed by a complete physical examination. The minimal required laboratory and special studies are x-ray of the chest, complete blood count, urinalysis, serological test for syphilis, blood type and Rh factor determination, and a vaginal cytological study for malignant cells. All patients over 45 years of age have an electrocardiographic tracing; those presenting symptoms of urinary stress incontinence or any other symptoms referable to the urinary tract are examined by the urologist. Cytoscopy and intravenous pyelography are performed in all cases of prolapse of long standing even though the patient does not complain of any urinary symptoms.[11] If the cervix shows any pathological changes or if the Papanicolaou slide is not normal, multiple biopsies are taken. Blood chemistry, glucose tolerance, liver function, and other special tests are ordered when indicated.

No effort is spared to place the patient in the best possible mental and physical condition prior to surgery. She is reassured and briefly informed of the preoperative, operative, and postoperative plan. If unduly apprehensive or unable to secure rest at home she may be brought into the hospital for four

*The opinions expressed are those of the authors and do not necessarily reflect the opinion of the Department of Defense. Cleared for publication by the Department of Defense Office of Public Information.

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or five days prior to the performance of the operation. Cervicitis and vaginitis are treated, cervical polyps are removed and submitted to the pathologist. Obesity, anemia, dietary deficiency, and urinary tract infection are treated to maximum response prior to operation. The patient with atrophic vaginal mucosa is often given a course of topical estrogens and those with dysfunctional uterine bleeding may benefit from a course of androgen therapy prior to operation.

All patients are admitted to the hospital at least twenty-four hours prior to surgery and are placed in bed for a rest. Enemas are given only on definite indication and not as a routine. A careful pelvic examination is performed to re-evaluate the pathology and to confirm the wisdom of the selection of operative procedure. Surprising changes, including those associated with intrauterine gestation, can occur within a few days' time! Following the pelvic examination the vagina is irrigated with 1:10,000 solution of potassium permanganate. A member of the anesthesia department then visits the patient to discuss the anesthetic agent with her and to assure himself that she is ready to receive an anesthetic. Every patient is cross-matched for 1,000 c.c. of whole blood, which accompanies the patient to the operating room and is given whenever the need arises.

Operative Technique

The technique to be described will be based in the main upon that originally advocated by Heaney.[12] Certain important modifications are added, however, these to be used in every case and not reserved for the occasional one with large enterocele or complete procidentia, as has been advocated from time to time.[13-16]

Subarachnoid anesthesia is preferred unless there is some contraindication. This is usually supplemented with a small amount of intravenous Pentothal sodium. Upon completion of injection of the spinal anesthetic agent, the patient is carefully placed in the lithotomy position, buttocks well down over the edge of the table, feet and legs suspended high in the air by slings about the ankles with no pressure exerted on the calves, knees, popliteal spaces, or thighs. The table is elevated to its full height, which allows the assistants to stand inside the legs without making any pressure on them, and to assist without undue strain and fatigue. As soon as anesthesia is obtained the table is placed in a 15 degree Trendelenburg position to facilitate light centering, exposure, and to aid in keeping the bowel out of the pelvis. The vagina, perineum, and thighs are scrubbed with tincture of green soap, flushed with sterile water, and painted with a mercurial antiseptic; the patient is catheterized and draped. The operator seats himself on a high stool directly in front of the operative field and a sterile draped Mayo stand is placed directly before him immediately below the patient's buttocks. This has been found to be most useful for those instruments which are used repeatedly. If the labia minora are redundant they are sutured to the skin of the adjacent thigh with one catgut suture. A bimanual examination is performed, the anterior lip of the cervix is grasped with a sharp tenaculum and the uterine cavity sounded, the cervical canal is dilated to admit a small sharp curette, and the endometrial cavity is thoroughly curetted.

Both lips of the cervix are now grasped with the tenaculum and the cervix is held downward while a circumferential incision is made completely around

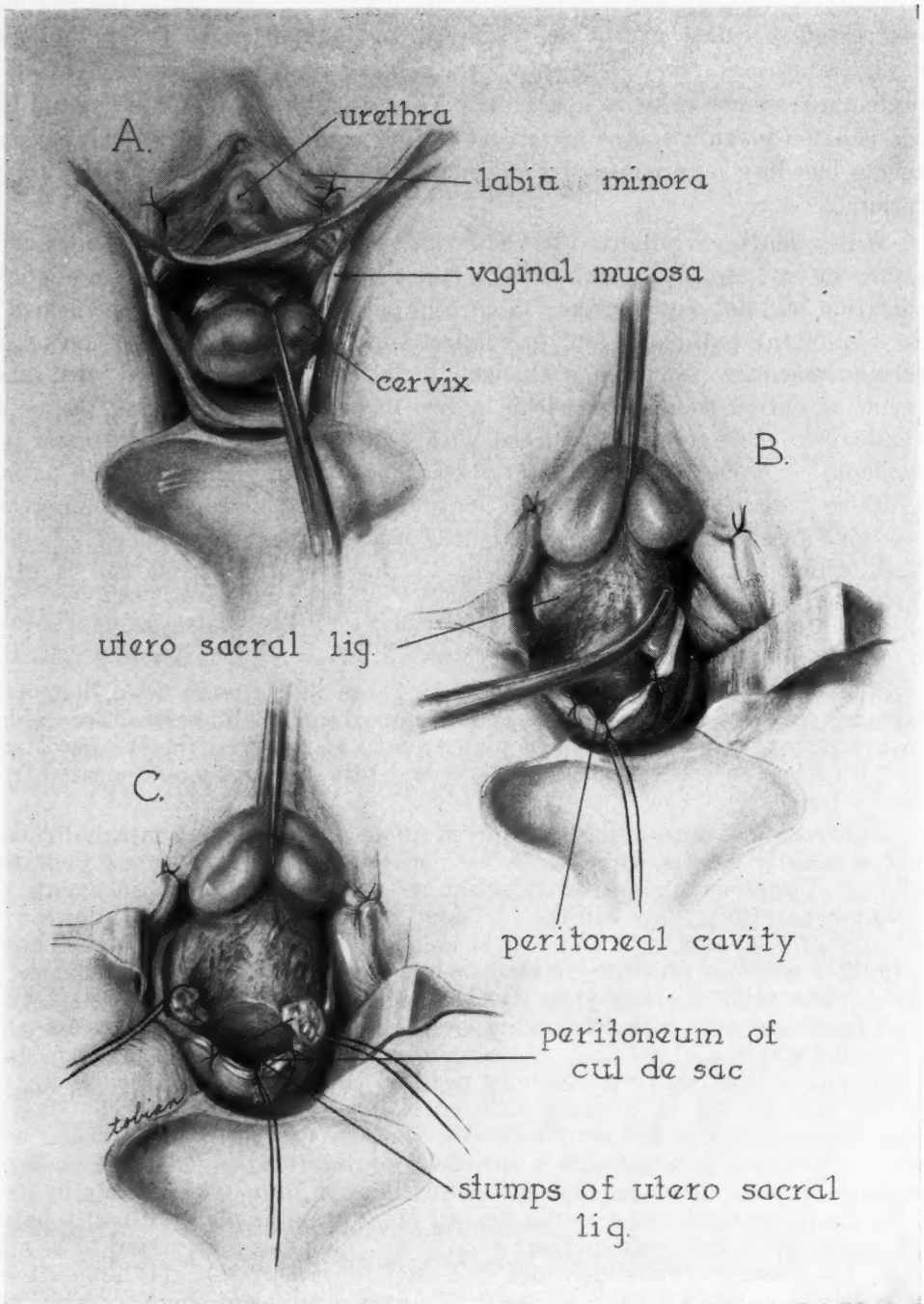

Fig. 1.—*A*, A circular incision has been made at the junction of the vaginal mucosa with the portio vaginalis of the cervix, preserving as much mucosa as possible. The mucous membrane alone is mobilized outward for a distance of about 3 cm.

B, The uterosacral ligaments are laid bare and are clamped with Heaney clamps. The posterior peritoneal sac has been opened, and the edge of the cut peritoneum has been coapted to the mucous membrane with three sutures.

C, The uterosacral ligaments have been clamped, severed, and ligated, and a second double-strand tie has been placed for traction.

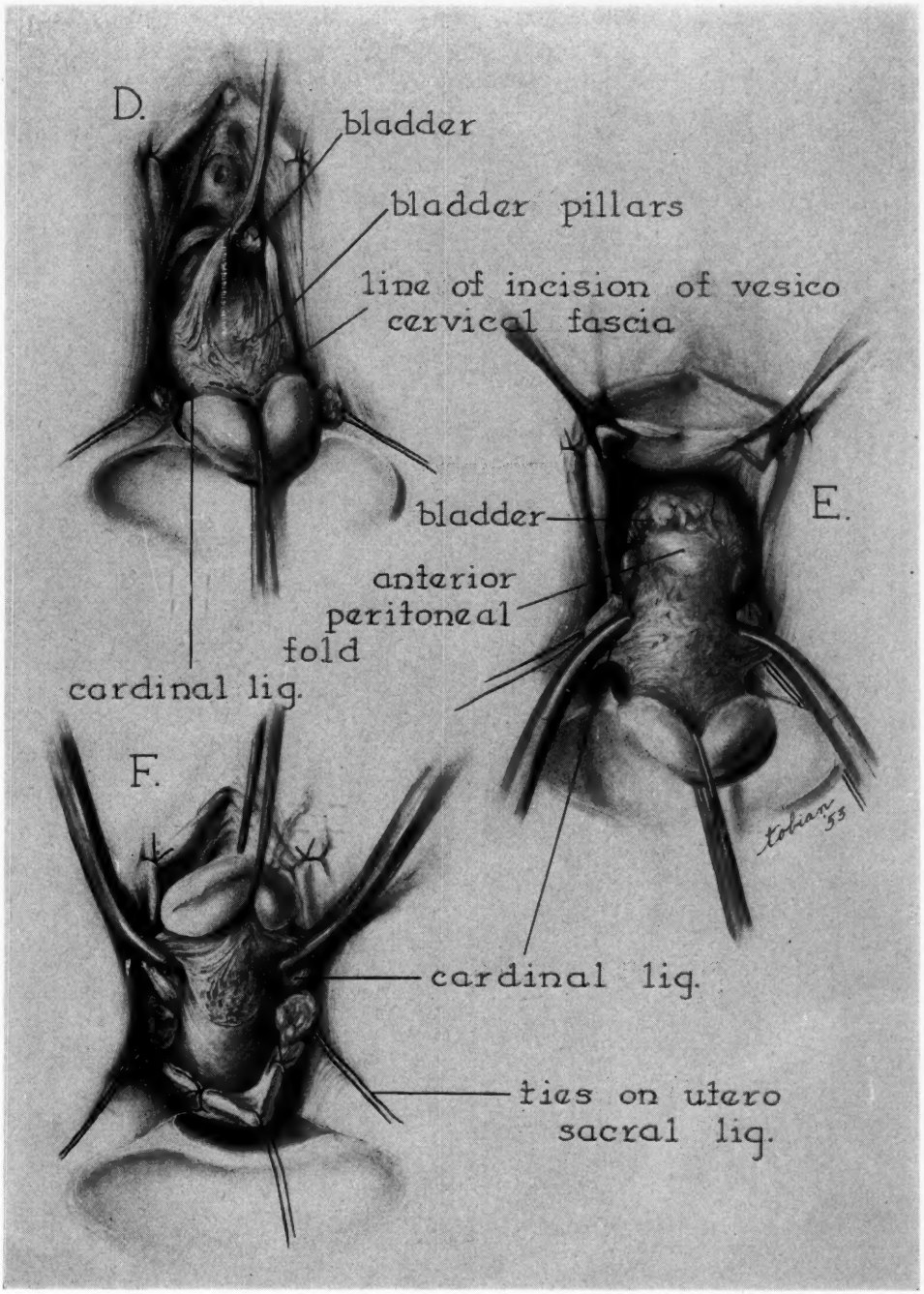

Fig. 1.—*D*, The vesicocervical fascia has been incised transversely and the bladder pillars have been partially stripped back from the cardinal ligaments by means of a gauze-covered finger. The Pennington clamp holds the lower margin of the bladder. Note the pillars only partially liberated on each side.

***E*, The bladder has been pushed up so that the pillars are completely retracted. The anterior peritoneal fold is visible at the lower bladder margin. Heaney clamps have been placed on both cardinal ligaments.**

***F*, Posterior view of Heaney clamps as placed on the cardinal ligaments.**

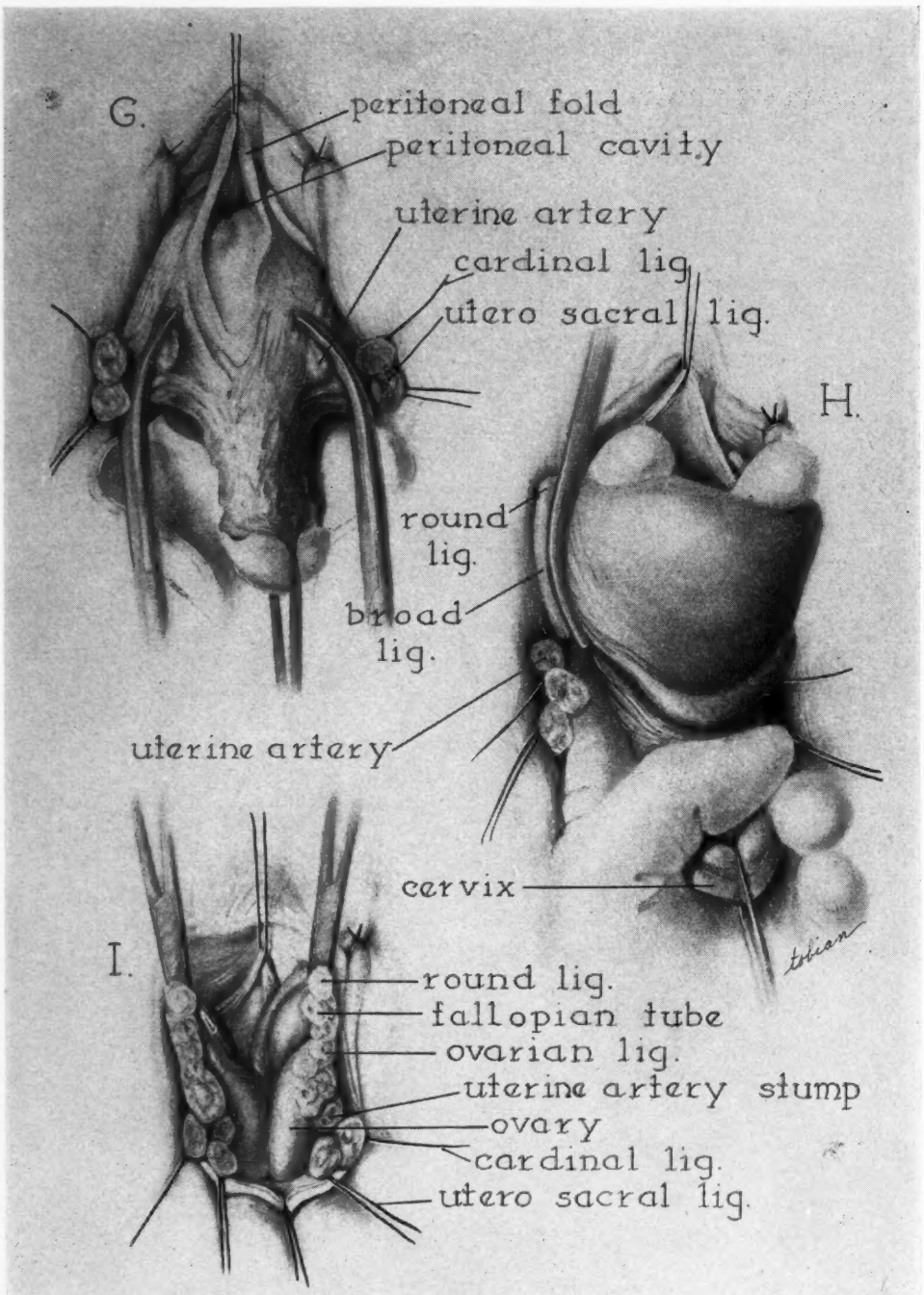

Fig. 1.—*G*, The cardinal ligaments have been severed and tied. Immediately below them is seen the double-strand traction suture on the uterosacral ligaments. The anterior peritoneal fold is now opened and is held upward by a traction suture. Heaney clamps have been placed across the knuckles of both uterine arteries.

H, The uterus has been delivered anteriorly and the Heaney clamp is placed across the entire right broad ligament. If this proves to be large, a second clamp would be inserted from below upward on the same side, dividing the ligament into two portions for tying.

I, The clamps are in place, and included from above downward are the round ligaments, Fallopian tubes, ovarian ligament, and upper broad ligament. The stump of the uterine artery is not included in this bite.

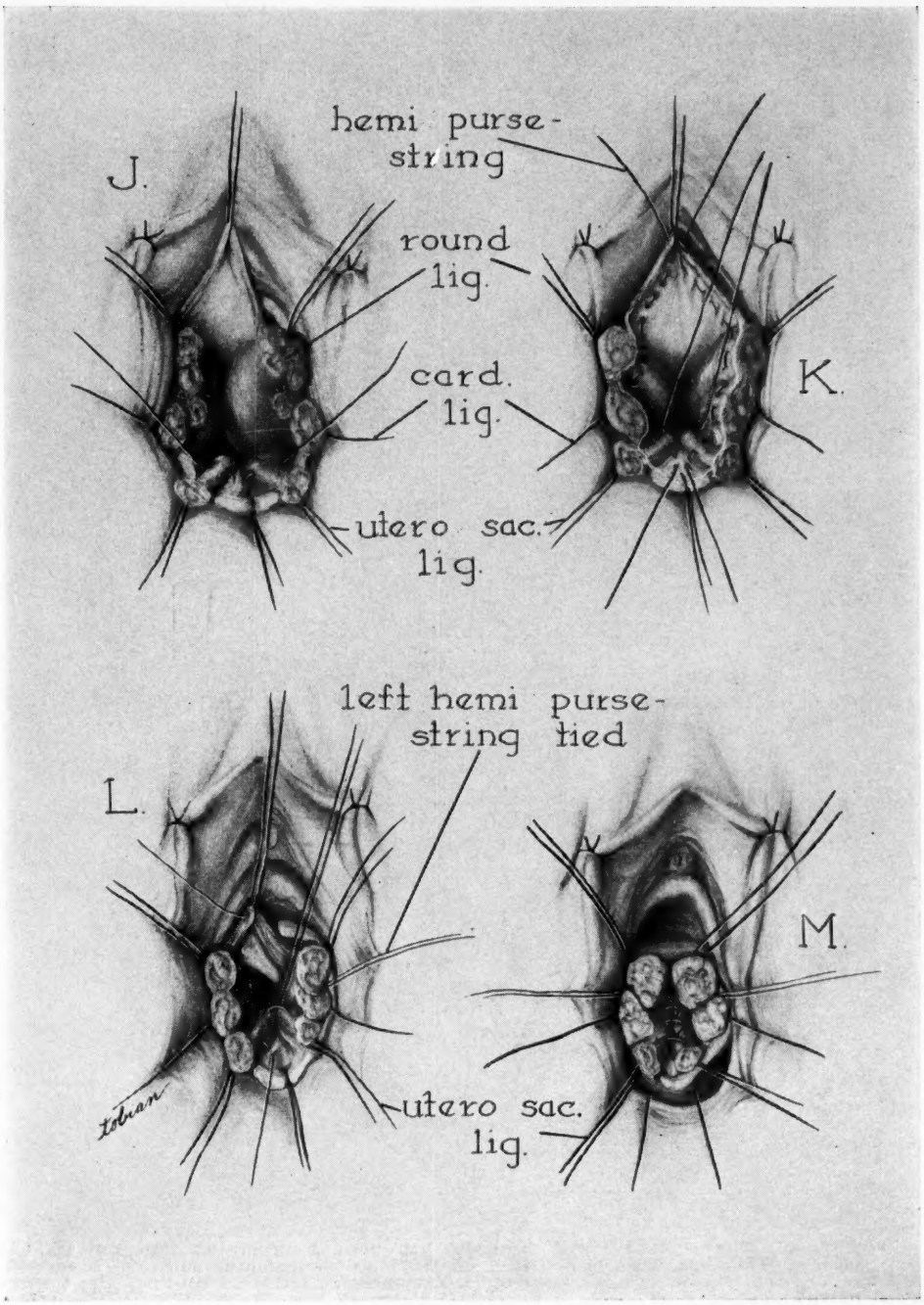

Fig. 1.—*J*, All pedicles are now ligated and are held downward and outward by secondary traction sutures. A chromic No. 1 suture has been inserted to coapt the two uterosacral ligaments. This is placed as high as possible in the cul-de-sac and is usually about 5 cm. from the cut end of the ligaments.

K, Two hemi-purse-string peritonizing sutures have been inserted near the peritoneal margin. The first uterosacral coapting suture is held upward.

L, The left hemi-purse-string suture has been tied, partially closing the peritoneal opening. The first uterosacral coapting suture has been tied.

M, The peritoneal cavity is closed. The uterosacral ligaments have been completely joined with three interrupted sutures, the last of which starts and ends on the posterior vaginal mucous-membrane surface. The traction sutures on the uterosacral ligaments will be tied to each other and cut.

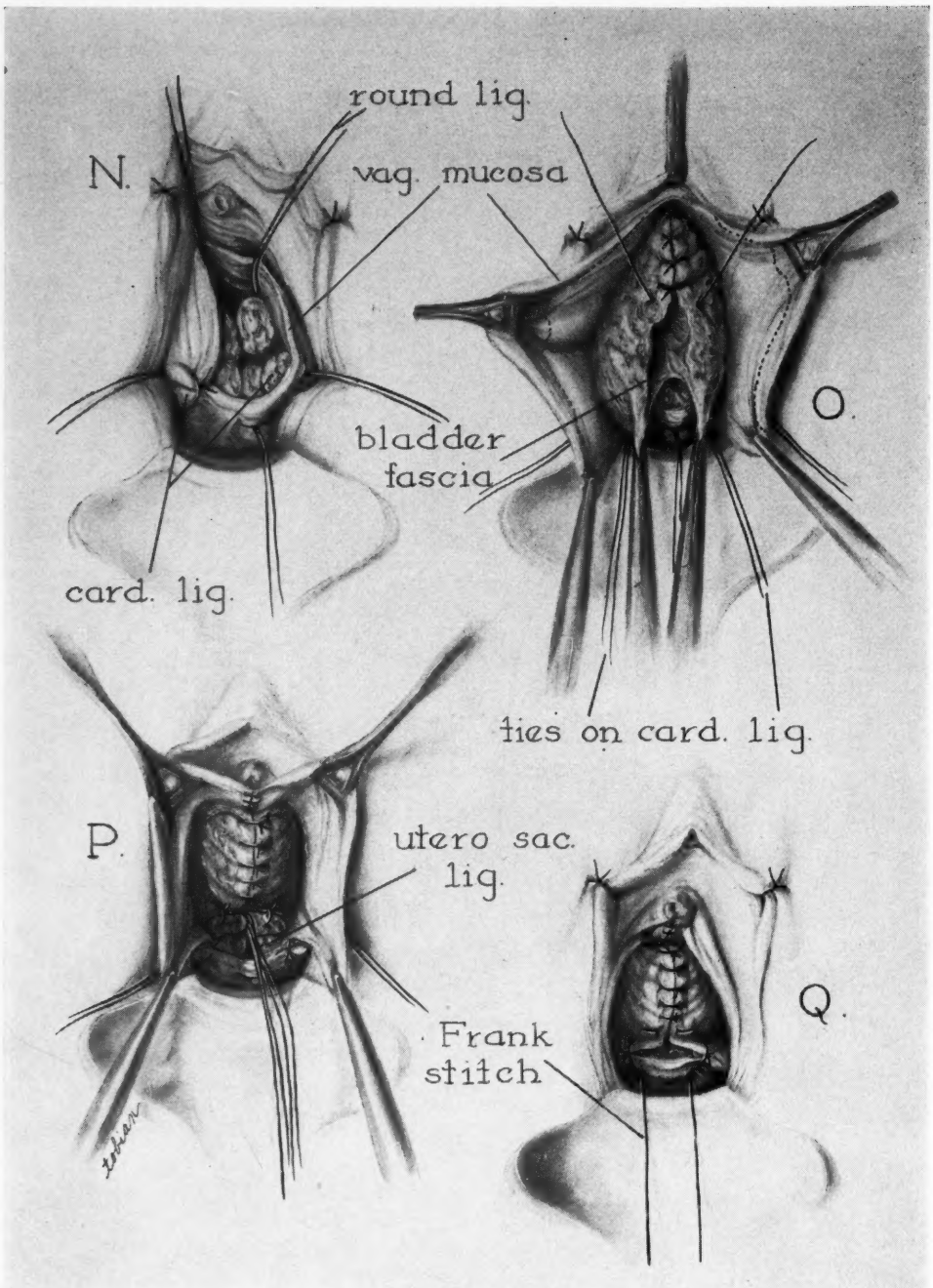

Fig. 1.—*N*, The right cardinal ligament has been incorporated into the right-hand vaginal corner. This suture starts and ends on the mucous-membrane surface. It is held for traction. A second suture has been inserted 1 cm. medial to this to continue the transverse closure of the vaginal vault. The left cardinal ligament has also been sewed into the left corner of the vagina. The two ties held upward are those from the stumps of the round ligaments.

O, The anterior vaginal wall has been completely dissected. The vaginal mucosa is held out laterally. The dotted line shows excess mucosa to be trimmed. Note the laceration of the fascia propria of the bladder which resulted in the cystocele.

P, The urethrocele and cystocele have been repaired with interrupted atraumatic sutures, and Kelly sutures have been placed at the urethrovesical junction. The round ligaments have been tied together and have been sutured to the posterior edge of the repaired fascia of the bladder.

Q, The transverse repair of the vaginal vault is being completed by means of a Frank stitch which starts in the mucous membrane posteriorly, goes through the anterior mucous membrane, then across the edges, and reverses to end up posteriorly. The anterior vaginal wall and vault have been completely closed.

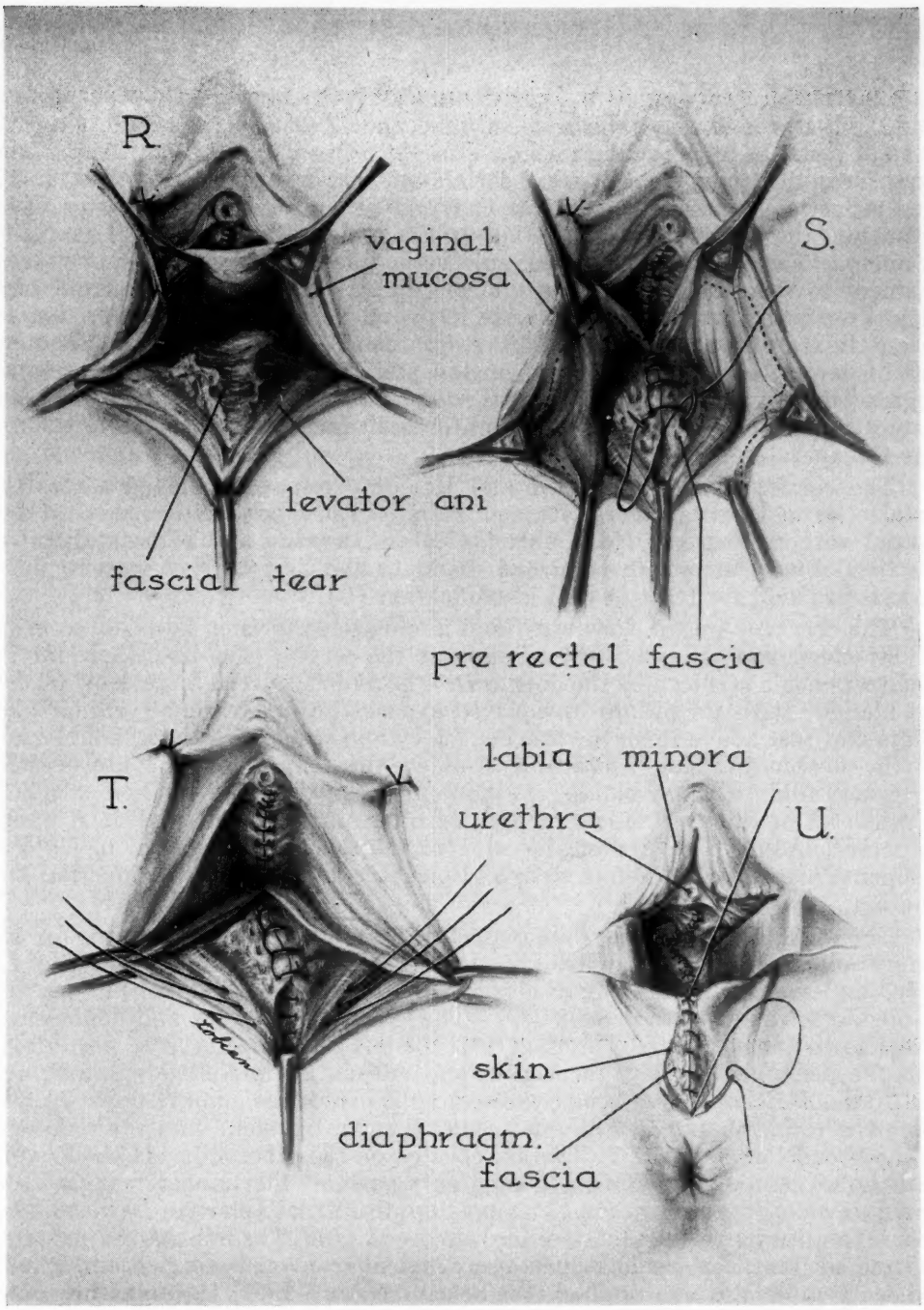

Fig. 1.—*R,* Allis clamps have been placed at the old margins of the hymenal ring, and the scarred tissue at the mucocutaneous junction between them has been removed with scissors. The mucous membrane of the posterior vagina has been dissected laterally and posteriorly up to the point of coaptation of the uterosacral ligaments. Note the laceration of the fascia propria which is responsible for the rectocele.

S, A midline incision has been made in the posterior vaginal mucosa. It is held laterally. The dotted line shows excess mucosa to be removed. The rectocele repair has been started with continuous lock sutures of No. 0 chromic catgut.

T, Three interrupted sutures have been placed in the levator ani muscles but are not tied until the upper mucous membrane is closed.

U, The redundant mucosa has been trimmed and the posterior vaginal wall has been completely closed with a running lock suture. The three levator sutures were tied prior to completion of the closure of the mucous membrane. A crown stitch has been taken in the sphincter cunei. This suture has been tied and is being held upward. The diaphragmatic fascia is closed with a running stitch which is to be reversed as a continuous subcuticular stitch and will be tied to the crown stitch. This completes the operation.

the junction of the vaginal wall with the cervical mucosa. This incision extends only through the mucous membrane and is made as near the external os as is possible to prevent shortening of the vagina. Using both sharp and blunt dissection the mucosa is freed for about 3 cm. in all directions (Fig. 1, *A*). This reflection exposes the cervical ends of the uterosacral and the cardinal ligaments, the peritoneum of the cul-de-sac, and the vesicocervical fascia or ligament. The peritoneum of the cul-de-sac is opened from one uterosacral ligament to the other and the peritoneal edge is coapted to the mucosal edge with three interrupted sutures, the one in the midline being held with a double-strand ligature for exposure. This stops the considerable and troublesome loss of blood from the widely opened posterior parametrium. One or two fingers are now inserted into the cul-de-sac and the pelvis explored as completely as possible to assure that no unforeseen factors are present to complicate the operation.

The cervix is pulled upward and Heaney clamps are placed across the distal ends of the uterosacral ligaments (*B*). The ligaments are severed and ligated with a suture of No. 1 chromic catgut, leaving ample tissue distal to the tie. A second suture is placed distal to the first and after tying both strands are held for traction and identification (*C*).

The cervix is pulled downward and a transverse incision is made, severing the attachment of the pubocervical fascia to the cervix. The line where the incision was made is shown by the dots in *D*. The gauze-covered finger now pushes the bladder with its pillars upward to expose the underlying cardinal ligaments and just above them the uterine artery and veins with the knuckle made by the descending and ascending arms of the loops, and the uterovesical peritoneal fold. Heaney clamps are now placed at the same level on each side to grasp all of the uterine end of each cardinal ligament but just short of the vascular bundle (*E*). A posterior view of the same step is shown in *F*. The ligaments are severed, double tied, and one strand held for identification and traction.

The anterior peritoneal fold is opened and caught with a suture for exposure and identification. Heaney clamps are placed across both uterine arteries and veins, keeping fairly close to the sides of the corpus but leaving ample tissue distal to the clamp (*G*). The vessels are severed and double tied. This ligature is not held. The fingers of the left hand are inserted posteriorly into the peritoneal cavity, the cervix and corpus are pulled downward, and the fundus is delivered anteriorly. A clamp is placed from above downward to catch the round ligament, Fallopian tube, ovarian ligament, and the remnants of the broad ligament (*H*). This is repeated on the other side. If the amount of tissue seems too great for one clamp, only one-half the tissue is caught from above downward and a second clamp is applied from below upward on each side. The uterus is now cut free and removed (*I*). The adnexa are palpated and pulled down for visual inspection; surgical removal is carried out if indicated. Double ties are applied, the second being looped through the round ligament and held with two strands for traction and identification. Any enterocele sac is dissected out and excised.

One of the most important of all procedures in the repair to prevent prolapse of the vault or later recurrence of symptoms is to suture together the uterosacral ligaments, commencing as far back in the pelvis as is possible. Traction is made on each uterosacral ligament and a chromic No. 1 suture is placed as high as possible around each ligament including several small bites of the peritoneum of the lower cul-de-sac. This suture is not tied at this step but held for exposure (*J*). A purse-string suture of plain No. 1 catgut is inserted on the left commencing at the midline anteriorly and ending at the midline

posteriorly, catching frequent small bites of the peritoneum only. This suture is held, not tied, and a similar hemi-purse-string suture placed on the right side (*K*). The suture placed in the uterosacral ligaments is tied and cut, the left hemi-purse-string suture is tied and held (*L*). The right hemi-purse-string suture is tied and held. Now the two hemi-purse-string sutures are tied to each other and cut. If it is desirable to leave a drain in, one is placed in the peritoneal cavity just before the hemi-purse-string sutures are tied to each other. The peritoneal cavity is completely closed; the ends of all ligaments and tissue stumps lie in the extraperitoneal space. The distal portions of the uterosacral ligaments are now joined to each other from just anterior to the rectosigmoid to the posterior vaginal wall with three or four interrupted sutures, the distal one of which includes the mucosa in the midline (*M*). The latter tie is held for traction and to identify the midline.

The left cardinal ligament is sutured into the left lateral angle of the vaginal vault, the suture being tied on the mucosal side and held; the right is treated in a similar manner. Traction is made on all three of these mucosal sutures and a suture inserted midway between the midline and the lateral angle on each side (*N*). The amount of anterior wall redundancy is now evident. The anterior mucosa is freed by sharp and blunt dissection in a superficial plane so as to leave all of the vesicle fascia on the bladder. If there is relaxation of the anterior wall of any significance this dissection is continued to within about 5 mm. of the external urinary meatus. The dissection is also carried laterally to free the entire base of the bladder and both lateral walls of the urethra. The fascial defect under the urethra is next repaired with atraumatic chromic No. 00 catgut sutures, using an interrupted Lembert type of stitch. This repair continues up over the vesicle fascia as high as possible to give a long anterior wall (*O*). If the fascial defect is marked, a second row of similar sutures is placed over the first. If stress incontinence of urine was a complaint, two or three Kelly-type sutures are placed about the vesicourethral junction to restore the proper angulation there.

The traction sutures placed previously in the round ligaments and held are now tied together, joining the ends of the round ligaments to make a sling under the bladder fascia; two interrupted sutures are placed through the posterior edge of the repaired fascia into the round ligaments to close off completely the fascial platform on which the bladder now rests (*P*). The excess mucosa is trimmed off (dotted line *O*, usually more than is illustrated) and the anterior wall closed with interrupted chromic No. 00 sutures, every third one catching the underlying fascia. The apex of the vagina is closed with a Frank type suture (*Q*).

The posterior repair routinely extends the entire length of the vaginal wall as anything less than this predisposes to a recurrence of the prolapse. The ends of the hymenal ring are grasped with Allis forceps, the intervening scar tissue is excised at the mucocutaneous junction, and the mucosa is then freed by sharp and blunt dissection up to the point where the two ends of the uterosacral ligaments are sutured into the vaginal wall. This dissection is made immediately under the mucosa so that the pararectal fascia is preserved as a distinct layer over the anterior rectal wall; the dissection extends laterally far enough to expose intact pararectal fascia and the fascia covering the pubococcygeal portion of the levators (*R*). The fascial defect is now repaired with a running lock suture of chromic No. 00 catgut, which commences just below the ends of the uterosacral ligament and extends to the fascia of the urogenital diaphragm (*S*). All redundant mucosa is excised (*S*).

The pubococcygeal portions of the levator ani muscles are now caught with three chromic No. 1 sutures. These are held but not tied at this time. A run-

ning lock suture is placed to close the vaginal mucosa from above downward (*T*). As it approaches the levators it is held and the three interrupted levator ani sutures previously placed are tied without tension and cut. The suture of the posterior vaginal mucosa is now completed to the fourchette, tied, and cut. A running suture of chromic No. 0 catgut is started as a crown stitch, being placed with a wide sweep so as to catch the sphincter cunei and transverse perinei muscles on each side. It is tied and the end held while the suture continues as a running one to catch the diaphragmatic fascia. At the anal end the suture is locked and then continued back as a subcuticular stitch to its original end where it is tied and cut short (*U*).

During the operation whole blood is used in adequate amount to replace any significant loss, usually any over 250 c.c.

Postoperative Care

Careful and painstaking postoperative management is essential to the attainment of good operative results and to the avoidance of complications. Immediately upon completion of the operation a Foley catheter is inserted into the urinary bladder, to remain usually for seventy-two hours if complete anterior wall repair has been done. This step probably is unnecessary with an adequate and experienced nursing staff but it is a good preventive for overdistention. After removal of the catheter a daily postvoiding catheterization should be performed until the residual urine is less than 45 c.c. Immediately following insertion of the catheter the vagina is packed lightly but firmly with gauze which is removed twelve hours later. This pack obliterates dead space and helps to prevent hematoma formation.

The legs are removed from the straps and elastic bandages are applied from the toes to the groin before the limbs are lowered. This increases the circulation blood volume by about 500 c.c. and prevents the shock-like picture so often seen when the patient is moved from the lithotomy and Trendelenburg position to a level one. We also feel that this application helps to prevent venous stasis, an important prophylactic feature in the avoidance of thrombosis and embolism. These bandages are allowed to loosen themselves and are not removed until twenty-four hours later. Nothing is given by mouth until auscultation of the abdomen reveals the presence of active peristalsis, usually within twenty-four to thirty-six hours. During this period adequate intravenous glucose solution is administered to ensure a urinary output of 1,500 c.c. or more per twenty-four-hour period.

We have used routine postoperative antibiotics in an endeavor to reduce postoperative morbidity. Penicillin and streptomycin yielded only fair results. In more recent months patients have received 500 mg. of Terramycin intravenously every twelve hours in a glucose infusion. This is followed by 500 mg. by mouth every six hours as soon as the patient is placed on oral feedings. This type of prophylactic therapy definitely reduces morbidity and promotes healing; it thus adds to the patient's postoperative comfort and reduces the hospital stay. We feel that it is worth while although we have not used it on enough patients to have any statistically significant results; the one objectionable feature is a fairly high incidence of nausea and diarrhea.

Patients are encouraged to move freely and breathe deeply during the first twenty-four hours and to ambulate during the second twenty-four. Patients are observed closely in the immediate postoperative period as many postoperative complications can be prevented by frequent and accurate observations of the patient by the surgeon or one trained in the particular surgical technique employed. A warm oil retention enema is given on the evening of the third day and thereafter milk of magnesia or enema only as requested by the patient or specifically indicated.

From October, 1951 to May, 1953, there were 40 patients at the Tripler Army Hospital managed with the preoperative, operative, and postoperative measures herein described. Since May, 1953, 30 additional patients were operated upon at the United States Naval Hospital, Chelsea, Massachusetts. Nearly all of these patients presented the primary complaints and findings associated with genital prolapse of varying degrees; all of them had failed to respond to the usual conservative procedures. This number is too small to be significant statistically but we were impressed by the uniform excellence of the anatomical and functional results obtained. Symptomatic relief was achieved in nearly 100 per cent of the patients; those complaints not cured by the operation were much alleviated. There were no shortened vaginas and not a patient complained of dyspareunia.

Summary

An operative technique for vaginal hysterectomy has been presented in detail with the use of illustrations to clarify certain steps which often are obscure to the neophyte. The technique is based on that originally described by Heaney but certain modifications are presented in the belief that they should be applied to every case and not reserved for the occasional one. Emphasis should be placed on the following: (1) preservation of all vaginal mucosa possible; (2) reflection of the mucosa in a superficial plane for ease of dissection and to minimize blood loss; (3) postponement of the anterior dissection until the uterus has been removed and the vault partially closed; (4) suture of the peritoneum of the cul-de-sac to the posterior vaginal cuff; (5) free mobilization of involved tissues and exposure of anatomical planes; (6) placement of clamps so as to leave ample free tissue protruding beyond the ends (never use the first tie for traction but place a second pulley-type one); (7) avoidance of any traction on the vascular stumps; (8) coaptation of the uterosacral ligaments through their entire length; (9) closure of the peritoneum with two half-purse-string sutures; (10) joining together of the round ligaments to form a sling under the bladder; (11) closure of the anterior mucosa with interrupted sutures, every third one of which is anchored to the underlying fascia; and (12) dissection of the entire length of the posterior vaginal wall with an anatomical repair from the vault downward through the perineum.

Conclusions

When operative relief for relaxations of the pelvic floor is indicated, a vaginal hysterectomy with other indicated reparative procedures gives excellent anatomical and functional results. Where a choice is necessary between the vaginal and the abdominal approach for hysterectomy, the former offers many advantages. Better results are obtained with a properly performed vaginal hysterectomy with associated repairs than are possible with the so-called conservative procedures.

A careful preoperative preparation of the patient, the precise application of a painstaking operative technique, and careful postoperative management all are essential to the attainment of good results.

The routine prophylactic administration of certain antibiotics both by vein and by mouth as a postoperative measure seems to promote clean wound healing, lessen the incidence of complications, and lower morbidity.

The illustrations were prepared by Jacqueline Tobian Steinmann, Medical Artist, 4614 Sunset Boulevard, Los Angeles, California.

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VAGINAL HYSTERECTOMY FOR UTERINE PROLAPSE

Incidental Pathology

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THERE is no unanimity of opinion concerning the best operation, nor is there any single operation which can be employed in all types of uterine prolapse. There are three essential factors, however, which should be considered in determining the operation to be chosen: (a) the age of the patient, (b) the desirability of conserving the childbearing function, (c) the presence of disease in the uterus or adnexa. The treatment of prolapse in the childbearing age and in cases where coitus need not be provided for, needs but little discussion. The operative procedures in these cases do not appear to be controversial.

In most instances uterine prolapse occurs in women who are beyond the childbearing age or who have had all the children they desire. In these cases, one of the following three principal operations may be used: (a) the Fothergill-Manchester type of operation, (b) the interposition type of operation, (c) the vaginal hysterectomy, and colpoperineorrhaphy.

The repair of the relaxed pelvic floor should be part of every operation for prolapse, although it is not always specifically mentioned.

There is general agreement today that uterine prolapse with a diseased uterus, functional or organic, should be treated by vaginal hysterectomy and colpoperineorrhaphy.[1, 2, 3, 4] It is in those cases where no uterine or adnexal disease is found on vaginal examination that many gynecologists today perform the Manchester or the interposition procedure. The latter operation, although it gives excellent results, makes the diagnosis and treatment of any future uterine bleeding difficult, if not impossible. In the recent follow-up of 705 cases of prolapse treated by interposition operation, Zacherl and Tischer[5] found pathologic bleeding in 10 per cent of their cases and malignant disease in 1.2 per cent of cases.

Modifications of the interposition operation in which the fundus and cervix (Spalding,[6] Richardson[7]) are removed prior to interposing the remaining portion of the uterus have been suggested. These operations are complicated and more time consuming than the vaginal hysterectomy and colpoperineorrhaphy without affording many of the advantages of the latter operation.

In a number of clinics, the vaginal hysterectomy has become a routine procedure in cases of uterine prolapse.[8, 9, 10] In others, it is performed only when uterine disease like myoma, functional bleeding, etc., makes removal of

the uterus desirable. This report covers a series of patients who had a vaginal hysterectomy for uterine prolapse, but in whom no uterine or adnexal disease was diagnosed prior to operation. The results of this study have further confirmed our belief in the advisability of removing the uterus, once it has fulfilled its reproduction function, during an operative intervention for uterine prolapse.

Material

The material studied consisted of 422 cases of uterine prolapse admitted to the French Hospital from 1940 to 1952, of which 227 were treated by vaginal hysterectomy and colpoperineorrhaphy. One hundred seventy-four of these patients had no other complaint than prolapse and on examination no evident uterine or adnexal pathology.

The age distribution of these patients is shown in Table I.

TABLE I. AGE DISTRIBUTION

AGE GROUP	NO. OF CASES	PER CENT
Under 40	41	23.5
41-50	73	42.0
51-60	45	25.8
61-70	12	6.8
71 and over	3	1.7

About 75 per cent of the patients were either premenopausal or menopausal. Besides the uterine prolapse, the patients studied had the following additional diagnoses: In 28 cases there were cervical lacerations and erosions. Prolapse of a "congenitally" elongated cervix without vaginal prolapse was reported in 9 cases. In only 6 cases was there second-degree prolapse alone. In all the remaining cases, uterine prolapse was associated with cystocele or cystorectocele with perineal relaxation. This group also includes 9 cases with the preoperative diagnosis of uterine fibroid in addition to prolapse. Following removal of the uterus, however, no fibroids were found.

The operative procedure employed in the cases reported was vaginal hysterectomy with anterior and posterior colporrhaphy and perineorrhaphy. The operations were performed by nine different surgeons. The technique followed was that described by the senior author.[11]

Pathology

In 114 cases 65.5 per cent uterine or adnexal pathology was found. In the other 34.5 per cent, normal uteri were removed and no significant pathology was observed in the adnexa.

1. Body of the Uterus.—The most frequent uterine pathology encountered was fibroids. These ranged from multiple small myomas up to a single fibroid 6 cm. in diameter. Twenty per cent of them were submucous in location. There were a total of 45 cases of fibroids, or a frequency of 25.8 per cent.

There were 37 cases of adenomysis (21.2 per cent). In 9 cases, a superficial adenomyosis was associated with fibroids. Endometrial polyps and polypoid endometria were encountered in 31 cases, i.e., a frequency of 17.8 per cent.

In two cases (1.1 per cent), adenocarcinoma of the endometrium was found on histological examination. These were postmenopausal women of 54 and 64 years of age, respectively. Their complaints were due to uterine prolapse and cystorectocele. Vaginal examination in both cases did not reveal

any abnormality except the prolapse and relaxation of the pelvic floor. In one of these cases, a routine vaginal smear done 5 months prior to admission to the hospital failed to reveal any malignant cells. In none of these cases was there any irregular spotting or bleeding. Since the diagnosis was not made until the pathological findings were reported, the adnexa were not removed.

2. Cervix.—Chronic cervicitis was present in 80 per cent of cases. There were also 15 cases of cervical erosion and 6 cases of unsuspected endocervical polyp.

3. Ovaries.—There were 6 ovarian cysts. These were: 1 dermoid cyst; 2 follicular cysts; and 3 serous cystadenomas. The pathology found in the 174 selected cases is shown in Table II.

TABLE II. PATHOLOGICAL FINDINGS IN 174 CASES

		CASES	PER CENT
Body of Uterus.—			
Myoma uteri		45	25.8
Myoma and adenomyosis		9	5.1
Adenomyosis		37	21.2
Endometrial polyp		31	17.8
Adenocarcinoma		2	1.15
Cervix.—			
Cervical erosions		15	8.6
Endocervical polyps		6	3.4
Tubes.—			
Chronic salpingitis		1	0.5
Ovaries.—			
Cysts		6	3.4
Dermoid	1		
Follicular cysts	2		
Serous cystadenoma	3		

Postoperative Course

The postoperative course in all cases was characterized by the absence of shock, low morbidity, and rapid convalescence. Our postoperative routine consists of early ambulation and retention catheter for five days. If the patient does not void following removal of the retention catheter she is catheterized every 8 hours; should she void she is catheterized once a day after voiding for the residual urine. Six grams of Gantrisin is given daily in divided doses until the urinary residual is 30 c.c. or less, when residual catheterization is stopped. In about 10 per cent of our cases (17 cases) we encountered urinary retention due to bladder atony which lasted from eight up to twenty-eight days following operation. Infections developed in 12 cases: These consisted of pneumonia in one case; cystitis in 6; pyelitis in one; thrombophlebitis in 3; and local infection in one case. There were 2 cases of postoperative bleeding from the vagina which were controlled by packing only. In one case, a broad ligament hematoma had developed but required no active therapy.

About 80 per cent of the cases have had a follow-up of from one to nine years. In only one case did we encounter a secondary enterocele. The follow-up of the 2 cases of adenocarcinoma of the cervix is not known to us. The results were otherwise gratifying both anatomically and clinically.

Comment

The surprising fact which emerges from this study is the high incidence of uterine and ovarian disease not accompanied by obvious clinical manifestations and not detected on pelvic examination.

The frequency of uterine fibroids, adenomyosis, and endometrial polyps in our series does not greatly exceed the frequency with which these conditions are generally encountered in gynecological material.

The frequency of uterine fibroids varies according to different statistics. Essen-Moller[12] reports a rate of 4.5 per cent of uterine fibroids in a series of 20,000 patients. Senator and Kaminer report a frequency of 11 per cent, while Welch's autopsy record as quoted by Kelly and Cullen[13] shows a rate of 20 per cent.

In order to ascertain the frequency of adenomyosis, 767 uteri removed for various indications in the French Hospital between 1950 and 1952 were studied. Adenomysis was found in 166 uteri, or a rate of 21 per cent. Hunter, Smith, and Reiner[14] report an incidence of 27 per cent of adenomyosis in 1,856 uteri removed for various gynecological conditions. It must be pointed out that the rate of adenomyosis in these last two series would be expected to be higher than in the population at random in view of the fact that these patients were operated upon for various gynecological complaints.

We had two cases of unsuspected adenocarcinoma of the fundus, a frequency of 1.1 per cent. This is a relatively high incidental finding. However, Codenhead,[15] reporting on 218 cases of vaginal hysterectomy for prolapse in the aged, observed 7 cases of uterine carcinoma at biopsy (3.2 per cent). Cofer and Evans[16] found, in 746 cases of vaginal hysterectomy performed for benign conditions, 4 cases of adenocarcinoma of the endometrium, one case of sarcoma, and 26 of cervical carcinoma. Falk[11] in his report of 500 cases of vaginal hysterectomy found 1.4 per cent of endometrial carcinoma and 0.4 per cent of endometrial sarcoma.

Among the gynecologists who do vaginal hysterectomies there seems to be a consensus that in uterine prolapse the uterus should be removed if it is diseased. Our present study seems to indicate that the uterus and adnexa have more than a 50 per cent chance of being diseased without manifesting clinical symptoms at the time of operation for prolapse. As a result of these findings, it is possible that some of the patients in the present series might have required further surgery if their uteri had not been removed at the time.

It is not the purpose of this paper to condemn the Manchester or interposition types of operation. In the hands of well-trained gynecological surgeons, however, the vaginal hysterectomy performed in conjunction with cystocele repair and perineorrhaphy is superior to the other procedures because: (a) it affords the removal of a diseased uterus or a uterus which is very likely to be diseased; (b) it precludes the development of carcinoma of the uterus or cervix; (c) it gives an opportunity to inspect the ovaries and tubes and remove any diseased part; (d) the operation is well tolerated, has a low morbidity rate, and a rapid convalescence; (e) vaginal hysterectomy and colpoperineorrhaphy give excellent anatomical and clinical results.

Summary

1. The incidental pathology found in 147 vaginal hysterectomies performed in patients with uterine prolapse and no other symptoms is reported.

2. Vaginal hysterectomy and colpoperineorrhaphy are suggested as the procedure of choice in the treatment of uterine prolapse.

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INCONTINENCE OF URINE IN THE FEMALE: EFFECTIVE RESTORATION AND MAINTENANCE OF SPHINCTER CONTROL*

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(From the Woman's Hospital in the State of New York)

PRIOR to 1849, the vesicovaginal fistula was considered the twenty-four-hour-a-day affliction. Then Sims, after many discouragements and trials, succeeded in curing a fistula. His techniques were made possible by his determination to solve this problem, and the silver-wire suture played a part in the success which crowned his efforts.

Today, it is the incontinent patient who presents us with a problem which has eluded a cure despite all methods available. Exercises of various sorts and repeated operations using the same or varying methods often fail to relieve her.

A number of opinions have been expressed as to the essential points of operations for the restoration of urinary continence. Jeffcoate,[1] commenting on his findings in an Aldridge[2] sling operation, states that, when continence is achieved, the posterior urethral vesical angle is restored and the urethra makes a definite angle with the bladder wall posterior to it. Hodgkinson[3] in his carefully conceived paper says, "Three factors appeared of importance in urinary incontinence in the female. The most important was the intact sphincter mechanism. In the nullipara, the internal urinary meatus from its dependent location was required to support full hydrostatic pressure. The second factor was related to hydrostatic pressure. The third factor of importance was the mechanical effect produced by downward and backward rotation of the bladder on the fixed or relatively well supported urethra." In previous papers, I[4] have stressed complete separation of the bladder and the urethra from all connection with the anterior vaginal wall and even with the cervix and urethra. That is an absolute necessity in every method. Plication and replication of the inferior urethra and the bladder now seem to me to be an incomplete procedure, for this fails to attack the problem at the point of greatest action.

Center of Control and Urination

The center of urethral activity is at the junction of the trigone and the inferior urethral wall, between the two insertions of the muscle of micturition.[5] This portion of the urethra, under the trauma of labor, slides and spreads laterally to re-adhere in "pancake" fashion to the relaxed, less elastic anterior vaginal wall. This leaves the internal meatus oval instead of circular, and

*Presented at a regular meeting of the New York Obstetrical Society, Oct. 13, 1953.

renders the urethra potentially incontinent. The center of control is definitely in the inferior wall of the internal meatus.

Normal control of the urethra is maintained by the sympathetically innervated circular smooth muscle surrounding the internal meatus, assisted by the voluntary pudendally innervated vaginal portion of the levator muscle. A hydrostatic pressure resistance of about 30 cm. of water exists in the urethral canal.

Normal urination, the reverse of normal control, is voluntarily brought about by the pudendally innervated muscle of micturition,[5] assisted by the parasympathetically innervated longitudinal smooth muscle. The hydrostatic pressure resistance then falls to zero in the urethral canal.

It is perfectly clear to me that since loss of control is initiated at this center, then restoration of control must be undertaken at this same center. Ideally, I consider that normal control depends on the circular smooth muscle's being maintained at or near its minimum length and being surrounded by some nonelastic sheath.

Suture

No such nonelastic sheath being available, some form of suture was contemplated, such as catgut, silk, nylon, membrane,[6] or silver wire. Silver wire, since maintenance is of paramount importance, was the first suture used. This suture should "roughly" ensheath the inner two-thirds of the urethra and should be able to lengthen if a sound were passed into the urethra.

Minimum Requirements

The minimum requirement is the least dissection required to replace the bladder in a normal position and to restore continence to the patient. This necessitates a complete separation of the urethra and bladder from the anterior vaginal wall, the cervix, and the uterus. If a patient has been operated upon previously, one may find it very difficult to separate the bladder from the vaginal wall abdominally. One should then separate all adhesions vaginally, reconstruct the vaginal wall, shorten the levator support of the urethra, and then do the operation to be described.

Two questions may be asked: (1) Will it be necessary to carry out my originally described operation first? The answer is in the negative unless it is necessary to separate adhesions and raise the bladder. (2) Will the operation herein described be sufficient in itself to restore continence? The answer is now in the affirmative.

The Operation

After a Foley catheter has been inserted into the bladder and the patient prepared for a suprapubic operation, then one should proceed as follows:

1. Make a low Pfannenstiel incision through the fascia of the rectus muscles, and enter the space of Retzius (Fig. 1).
2. Make a cystotomy incision (Fig. 1), if adhesions are dense, to facilitate the separation of the urethra and bladder from attachments to adjacent structures.

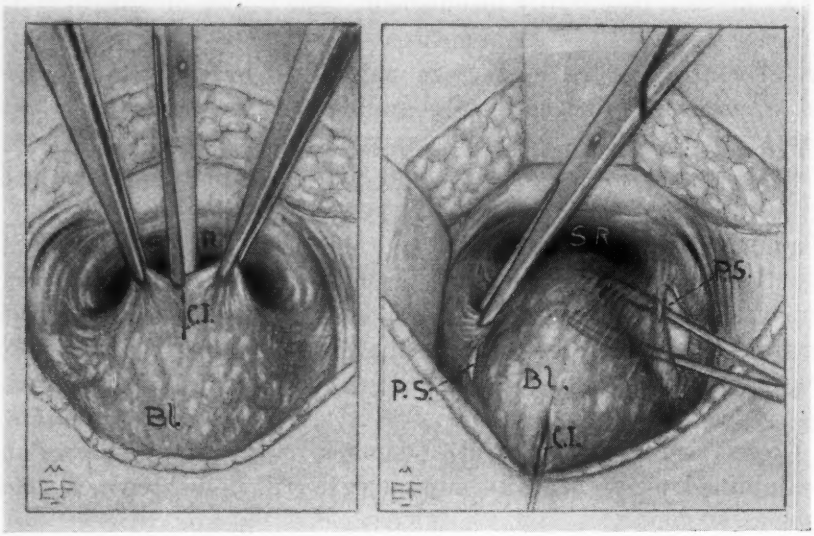

Fig. 1. Fig. 2.

Figs. 1 and 2.—Illustrate *S.R.*, the space of Retzius. *C.I.*, a cystotomy incision, and *P.S.*, the incisions to open the paravesical spaces.

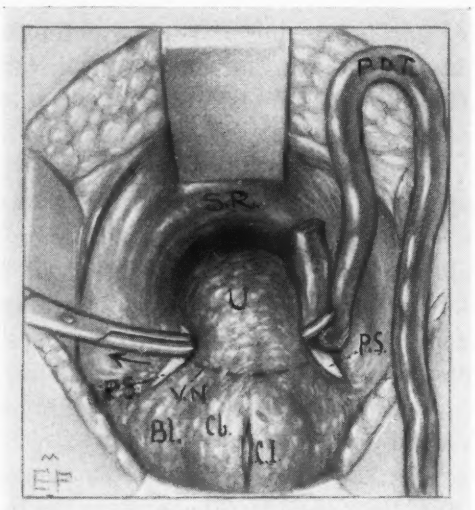

Fig. 3.—Illustrates *V.N.*, the vesicle neck; *Cb.*, the bulb of the Foley catheter, and *P.D.T.*, a penrose drain tube being passed under the inner third of the urethra, *U*, to elevate it.

3. Enter the paravesical space (*P.S.*, Fig. 2) on each side in order to separate freely the urethra and bladder from the anterior vaginal wall.

4. Pass a Penrose drain tube (*P.D.T.*, Fig. 3) around the urethra for traction. When there is no traction on the Penrose drain tube (Fig. 4) one sees the relaxed damaged urethral sphincter and when traction is applied to the tube (Fig. 5) one sees the normally functioning urethral sphincter.

5. Pass a No. 26 pure silver wire (Fig. 6) under the urethra, then over, picking up a small bite of the urethral wall (Fig. 7), around again, picking up another small bite (Fig. 8) and around again picking up another bite (Fig. 9). Cut the ends about one inch from the urethra after adjusting the wire loosely around the urethra.

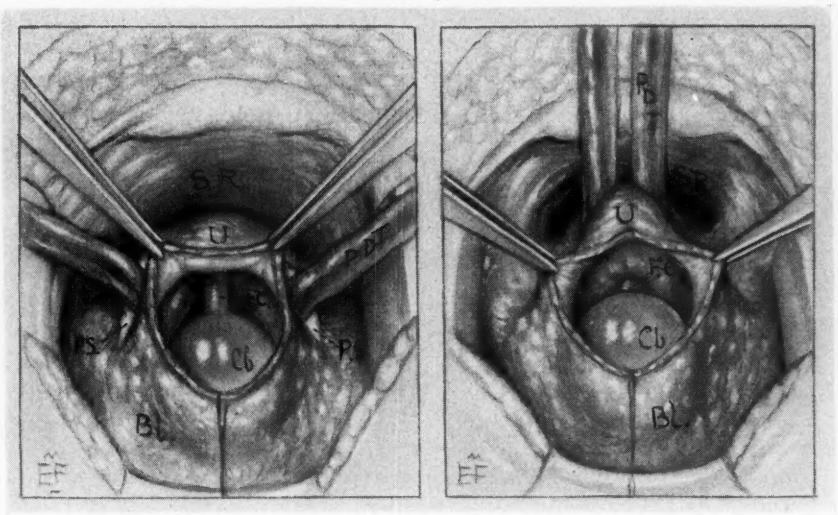

Fig. 4. Fig. 5.

Fig. 4.—Illustrates the relaxed, damaged urethral sphincter.
Fig. 5.—Illustrates the normally functioning urethral sphincter.

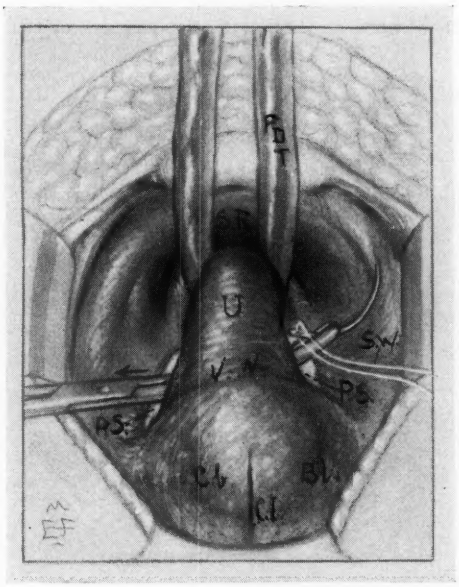

Fig. 6.—Illustrates a strand of No. 26 pure silver wire, *S.W.*, being passed under the inner third of the urethra close to the internal meatus.

6. Pass a second wire (Fig. 10) similarly around the urethra about 1½ to 2 cm. nearer the external meatus of the urethra.

If, after operation, it is found expedient to pass a sound in the urethra, the wires will slip to make the wire surrounding the urethra longer. If the wires do not encircle the urethra loosely, the internal meatus and trigone may be raised too high. A "bar" may form which may later require electrosurgery.

7. Close the cystotomy incision with interrupted No. 00 plain catgut sutures.

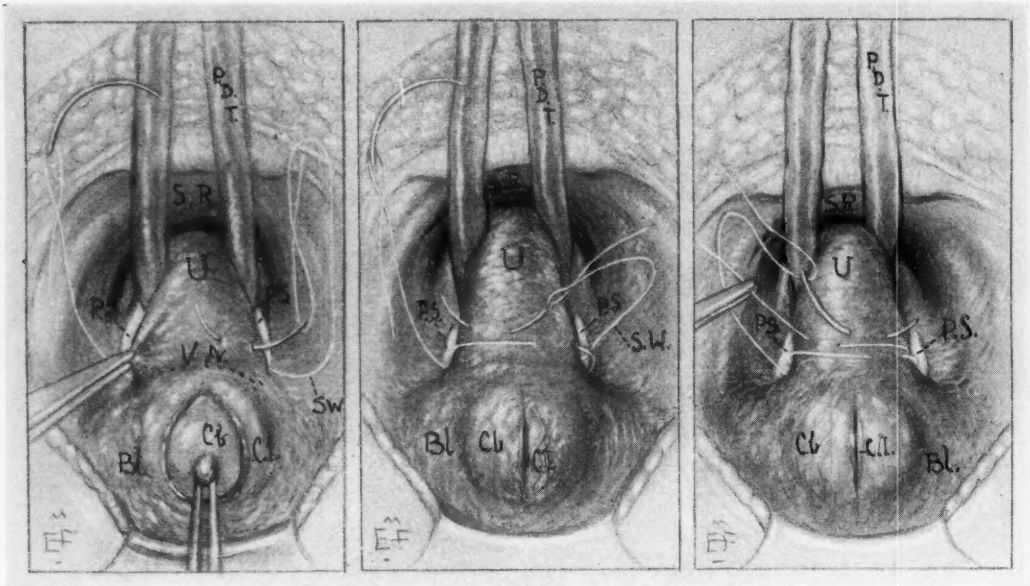

Fig. 7. Fig. 8. Fig. 9.

Figs. 7, 8, and 9.—Illustrate the continuing passage of the same silver wire.

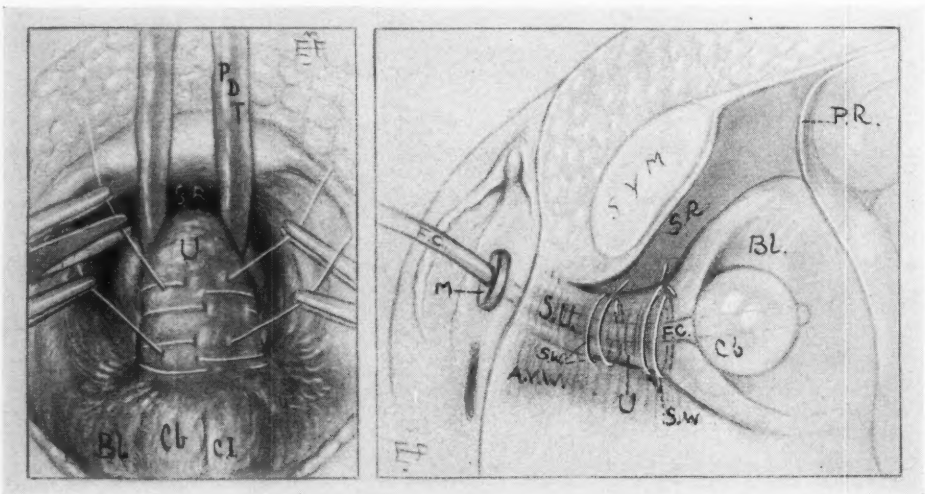

Fig. 10. Fig. 11.

Fig. 10.—Illustrates two silver wires encircling the middle and inner thirds of the urethra.

Fig. 11.—Is a transverse "ghost" illustration of the two silver wires surrounding the urethra.

8. Pass a Penrose drain from under the urethra up through a stab wound below the incision.

9. Close the space of Retzius.

10. Close the abdominal incision in layers.

11. Remove the Foley catheter and replace with a Kennedy Vitallium catheter. Remove the catheter on the third or fourth day.

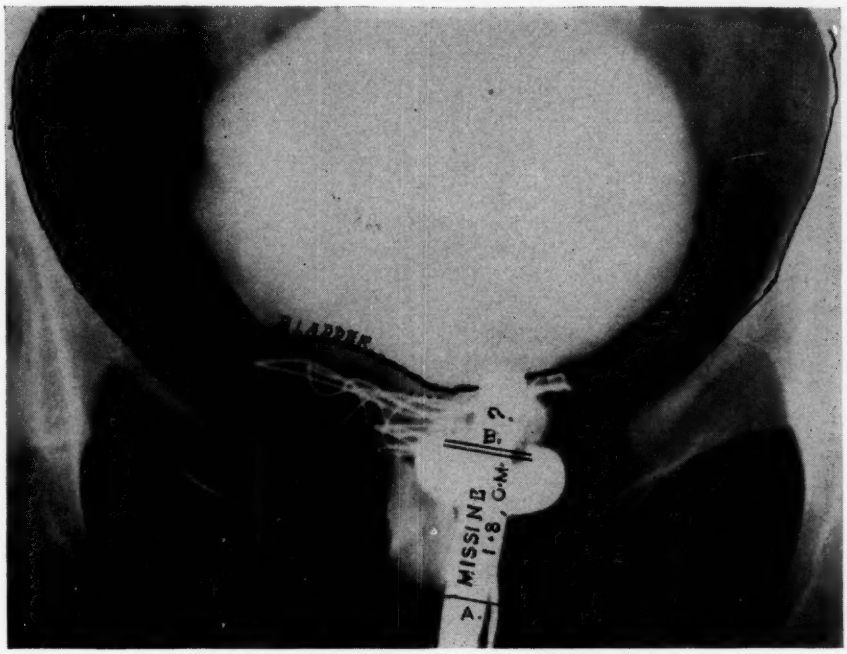

Fig. 12.—Illustrates the high level of the floor of the bladder, *B.*, the position of the present external meatus which is well up in the pelvis and *A* to *B*, the part of the urethra which the patient lost at delivery.

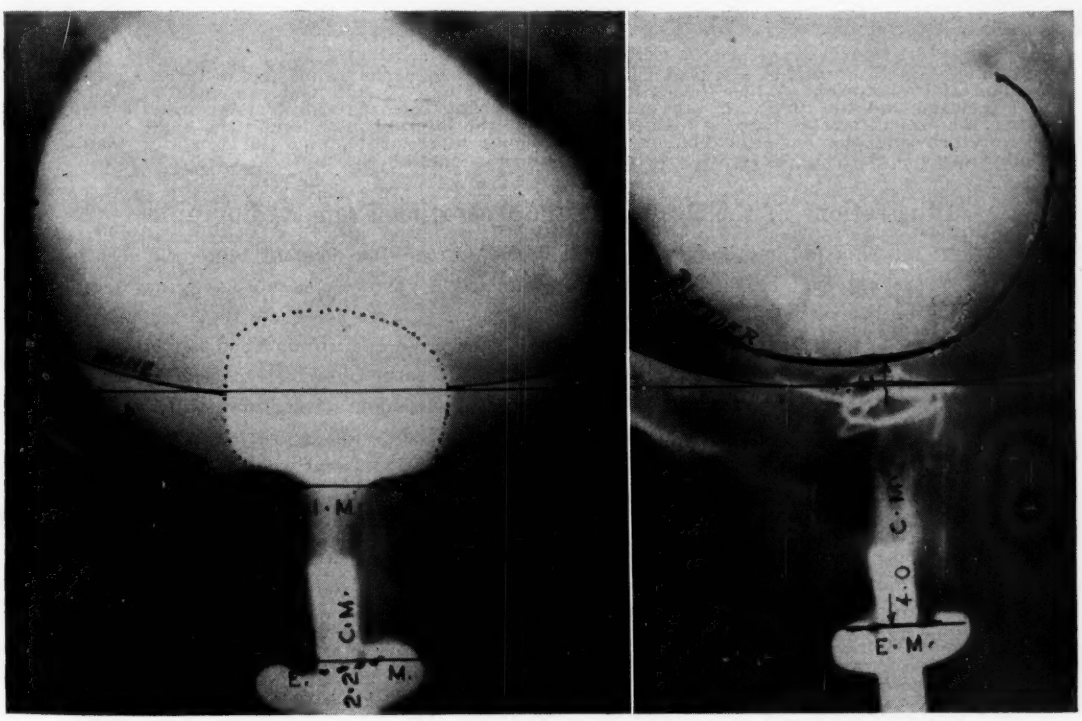

Fig. 13.—Illustrates: (1) the unusual replacement of the bladder floor into the pelvis, (2) the lift of the internal meatus, *I.M.*, and (3) the lengthening of the urethra from 2.2 cm. to 4 cm. The silver wire is shown surrounding the internal meatus.

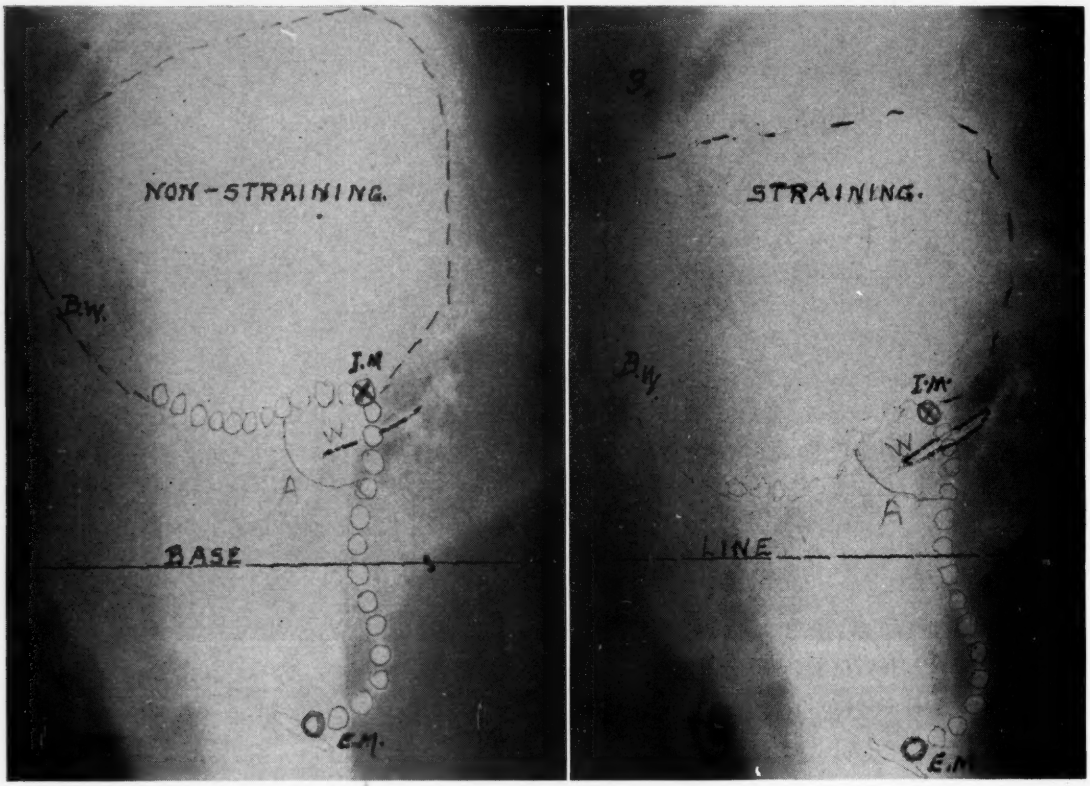

Fig. 14.—Illustrations are postoperative lateral radiographs using the metal bead chain method of Hodgkinson. When the patient is not straining, the *I.M.* (internal meatus) is high and forward and the angle, *A*, between the urethra and the posterior bladder wall is acute. When the patient strains there is little movement of the internal meatus and the angle between the urethra and the posterior bladder wall becomes more acute, and the posterior bladder wall rotates backward. Silver wires, *W*, are seen surrounding the urethra.

Illustrations of the Results of the Operation From Radiographs

CASE 1.—This patient had a tragic delivery. After five days of labor she lost her baby, lost the external half of the urethra, acquired a cystocele, a vesicovaginal fistula, a third-degree laceration of the pelvic floor, and a very large rectocele together with incontinence. She was referred to me and I have done three operations upon her, doing the plastic work, and each time I have tried to restore continence of urine. At each operation some gain was accomplished but the result was still most unsatisfactory. She gave me the opportunity to do another operation which I decided to do suprapubically and this method was used for the first time. Seventy-nine days after operation, a radiograph (Fig. 12) was made of the bladder. The anterior vaginal wall was very high and the external meatus was up behind the symphysis. Four months after operation she informed me that she was cured. Today, the anterior vaginal wall is unusually high. The vaginal orifice which was gaping before this operation is now as well involuted as that of any normal parous patient six months after delivery, and as well as being continent she is free from urgency and frequency.

CASE 2.—This patient had two operations before she was referred to me. Since then I have operated upon her four times with the result that she would have intervals of a few days of continence, but continence was spasmodic and very unreliable. After her seventh operation she had continence. Radiographs (Fig. 13), one made the day before

operation and the other nine days after operation, illustrate a marked elevation of the bladder floor; a great increase in the length of the urethra; the position of the silver wires surrounding the internal meatus.

Demonstration of the New Position of the Bladder

The Hodgkinson metal bead chain gives us very accurate information about: (a) the length, position, and mobility of the urethra; (b) the movement of the bladder wall and the internal meatus; (c) the contour of the bladder floor; and (d) the angle and change of angle between the urethra and its adjacent posterior bladder wall.

CASE 3.—The patient whose x-ray will now be shown had two previous operations for incontinence and, following each, incontinence became progressively worse. Five days after the operation performed by the technique described in this article she had a coronary thrombosis and was therefore not radiographed until five months later. The information obtained gives us a measure of the degree of maintenance which can be expected following this operation. Radiographs (Fig. 14) with the metal bead chain in the bladder and urethra were taken laterally, nonstraining and straining, five months after operation.

The radiographs were sent to Dr. Hodgkinson for his comment. In a personal communication,[7] he says: "My enthusiasm for your latest operation is high. I am very much impressed with the excellent vaginal repair you have achieved as evident from the high position of the bladder and the increased length of the urethra. On the other hand, the straining films demonstrate a very substantial downward and backward rotation of the bladder in relation to the relatively well fixed anteriorly displaced urethra. Such a set of circumstances for a patient suffering from urinary stress incontinence, in my very humble opinion, is most satisfactory. You have achieved the utilization of both principles. This certainly should satisfy Jeffcoate in that the posterior urethrovesical angle is restored and made more acute by the act of straining."

Conclusions

1. A close scrutiny of the anatomy and physiology of the bladder reveals that the active center of control and urination lies in the inferior wall of the internal meatus of the urethra between the two insertions of the muscle of micturition.

2. When this center is fixed: (1) with the muscle of micturition relaxed (sphincter closed), then voiding is impossible; and (2) with this muscle contracted (sphincter open), then voiding is continuous.

3. When incontinence begins, control diminishes at this active center, hence control must be restored here. The circular smooth muscle must be shortened to renew its strength and efficiency. The best approach seemed to be to pass a nonabsorbable, nonirritating suture of silver wire loosely around the inner two-thirds of the urethra.

4. Postoperatively, the urethra reattaches itself to the anterior vaginal wall, and rises into the pelvis; the bladder floor rises to, or above, the level of the bladder floor in the nullipara; the bladder can rotate backward, thereby diminishing the hydrostatic pressure on the internal meatus; the urethra makes an acute and not an obtuse angle with the adjacent posterior bladder wall; the anterior vaginal wall rises to an unexpected level; posterior urethritis and trigonitis frequently disappear in six to ten weeks.

5. Radiographs show that a damaged incompetent urethra can, by this operation, be made a competent urethra with the characteristics of the normal continent urethra in the nullipara; also that this restoration can be maintained.

I wish to express thanks to Dr. A. H. Aldridge, Chief Surgeon, to members of the Hospital Staff, and to Dr. F. P. Salvatore of the Resident Staff, for their interest and aid in this work. I also wish to convey my thanks to Dr. C. Paul Hodgkinson for his observations and wise comments through personal communications.

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Discussion

DR. JOHN ULLERY.—Perhaps to many of us Dr. Kennedy's descriptions of the physiology of micturition with the action of the internal urethral sphincter mechanism and the muscles of micturition seem complex. One must remember, however, that the whole problem of stress incontinence in the female is complex. I believe that his approach to these problems has been logical and has been based upon sound anatomic details.

The operative technique that he has previously described has been widely used both here and abroad and clinical results have substantiated its success.

He has mentioned Dr. Hodgkinson's work on the three factors involved in stress incontinence.

Dr. Kennedy's previous operative technique, as he has said, and as Hodgkinson has quoted, was aimed at restoring to normal the anatomy and physiology of the urethra and bladder. Cystourethrograms will also show that his previous operative technique has prevented the downward and forward thrust of the bladder and I believe also has prevented in a large number of cases the posterior rotation of the bladder itself. His operative plan described here adds another chapter in the over-all picture of our treatment of stress incontinence. I believe that it completes the treatment of the triad of factors that are involved in stress incontinence as described and emphasized by Dr. Hodgkinson, namely, an intact urethral sphincteric mechanism. It is logical to assume that the wire that is placed about the neck of the urethra involving the internal urethral sphincteric mechanism can complete this triad by restoring the sphincteric mechanism to normal. Perhaps there are other methods that might be used too. As I recall, Millen in 1948 opened the bladder and placed sutures through the bladder neck after removing a small wedge, to produce the same result. To me it seems that Dr. Kennedy's procedure is much simpler and probably much more effective. His presentation tonight, then, adds another chapter to enlighten us in the many problems of stress incontinence that as yet are unsolved.

DR. INGLIS F. FROST.—Dr. Kennedy has advanced a new principle in the treatment of stress incontinence by constricting the urethra without the necessity of a double operation from below and above. I am glad that Dr. Studdiford brought out the point that not all cases should primarily be operated on only from above, and to this I am sure Dr. Kennedy would agree, especially in those cases of stress incontinence that are complicated by a cystocele.

The figures as generally given of cure and failure by the vaginal route are about 75 per cent cure and 25 per cent failure. In uncomplicated cases where there have been

no previous operations and no adhesions, the cure rate should be at least 90 per cent or more. The remaining 10 per cent should be improved, but may need a subsequent operation from above the symphysis to complete the cure. Such an operation Dr. Kennedy has described.

When it comes to operating on any case of stress incontinence by the vaginal route, it is all important to know and find the cleavage planes in exposing the base of the bladder and the urethra. If these are not found, one is likely to court failure in not being able properly to place the invaginating urethral and bladder sutures. We are all familiar with the Kelly suture. This suture is supposed to be placed at the vesicle neck but many times, because of the failure fully to expose the vesicle neck, so that a mere denudation of the mucous membrane is done, the Kelly suture is likely to be placed haphazardly, thereby losing the proper constriction at the most essential part of the bladder.

In operating on these cases by the vaginal route it is important fully to mobilize the base of the bladder by following the cleavage planes, separating the base of the bladder from the anterior vaginal wall, from the cervix posteriorly, and laterally from the vaginal walls. The urethra should be thoroughly exposed and made free from its lateral adhesions. When this mobilization has been accomplished, the placing of the sutures at the vesicle neck can be accurately made and the other invaginating sutures in the urethra and bladder arranged in a proper order.

In nearly all cases of cystocele, the urethra tends to rotate under the symphysis and assume an angle of about 90 degrees. This must be restored to a normal 45 degree angle and lengthened as well. This restoration and lengthening of the urethra are what Dr. Kennedy has so often stressed. If one is not able to secure this from below then it is necessary to restore the urethral function from above and that is what Dr. Kennedy has so ably described tonight.

DR. THOMAS L. BALL.—I myself have never taken part in any study of the muscles of micturition but I think this Society should recall an original observation by one of its members, now very ill, Dr. Lynn L. Fulkerson, who thirty-one years ago described before the New York Academy of Medicine the sagging, sluggish bladder neck so characteristic of patients with stress incontinence. We now refer to the obliteration of the posterior urethrovesicle angle of Jeffcoate. Dr. Fulkerson many years ago pointed out to me and to other cystoscopists that when people are incontinent you can look in with a Fulkerson urethroscope or simple Kelly urethroscope and, if you watch the bladder neck, the posterior urethra and the base of the bladder will form a straight line. You can almost invariably pick out the patients who are going to be incontinent and those who are not. I think that any operation that restores the angle between the posterior urethra and the base of the bladder will cure the patient.

I should like to ask Dr. Kennedy whether or not his selection of suture material is not incorrect? No one approaches surgery of the bladder with a nonabsorbable suture material without some trepidation because if any material, whether it be silk, tantalum wire, silver, or linen, penetrates the urethral mucosa, it becomes the nidus of condensation of urinary salts at some time or other. Therefore, I wonder whether his operation could not be done with fascia to form the loops about the urethra.

DR. KENNEDY (Closing).—I would like only to answer Dr. Ball's question about the silver wire and its possible effect on the mucosa. I have tried to keep away from the mucosa as much as possible and confine its use to the muscular tissue. I have had one case where the silver wire cut through the inferior wall of the urethra and had to be cut. This patient could not void for several weeks, though a large catheter passed easily. Continence has since been restored.

THE EFFECTS OF DEMEROL AND TRICHLORETHYLENE ON ARTERIAL OXYGEN SATURATION IN THE NEWBORN*

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THIS study measures the effect of Demerol and scopolamine analgesia on the arterial oxygen saturation of normal full-term newborn infants, and the effect of trichlorethylene analgesia on normal full-term newborn infants. In previous publications we have reported chemical studies done on the capillary blood oxygen saturation of premature infants and of full-term infants. In one the effect of prematurity on blood oxygen saturation was measured[1] and in the other the effect of maternal anesthetic agents on the oxygen content of the infant's blood was determined.[2]

Materials and Methods

A double-scale, absolute-reading, alternating-current oximeter with an infant-sized earpiece was used in all determinations in the current study. The instrument† is devised for the photoelectric determination of absolute values of arterial oxygen saturation in the intact lobe of the human ear. Wood[3] of the Mayo Clinic has described the physical principles of the unit. Our results were not checked chemically, but previous work by other investigators[4] has shown the standard deviation of the difference between the photoelectric and Van Slyke determinations of the arterial blood oxygen saturation to be 2.9 per cent. In this study an attempt was made to obtain the first reading as soon as was possible after the head was delivered. As soon as an ear could be grasped, it was thoroughly cleansed with an alcohol sponge and then dried briskly with a gauze square. The earpiece was then applied and the necessary adjustments made on the oximeter. The first reading could usually be obtained within two minutes following delivery of the infant's head. Readings were taken every two minutes for thirty minutes after delivery.

Oxygen saturation levels were recorded on the infants of the following mothers: (a) fourteen who received no general anesthesia or analgesia; (b) thirty-seven who were given Demerol, 100 mg., and scopolamine, 0.4 mg., 2 to 4 hours before delivery and on whom regional anesthesia was used for delivery; (c) twenty-two who received trichlorethylene, 0.86 per cent to 1 per cent, self-administered by the patient for analgesia of labor and delivery. No other anesthesia or analgesia was used.

All infants studied were normal and from normal full-term pregnancies. Each infant cried spontaneously at birth, and was delivered either spontaneously or by outlet forceps delivery.

*This study was supported by the Playtex Park Research Institute.

†The machine is manufactured by Waters Conley Company, Rochester, Minn.

Results

Inspection of Fig. 1 shows that the 14 infants in the control series had an average arterial oxygen saturation level of 74 per cent two minutes after birth. All 14 of the infants cried spontaneously. The extremes of oxygen saturation measured from 53 to 94 per cent at birth. The average oxygen saturation level six minutes after birth was over 90 per cent and gradually climbed to 98 per cent by the end of thirty minutes.

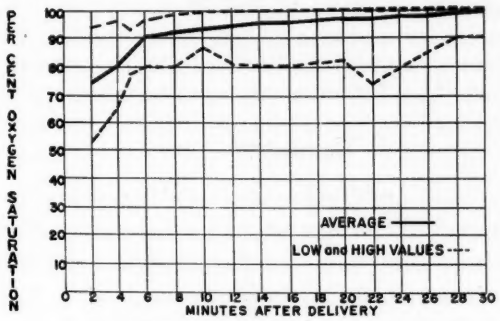

Fig. 1.—Oxygen saturation values were taken at two-minute intervals for the first half hour of life. None of these mothers had received general anesthesia or analgesia (14 cases).

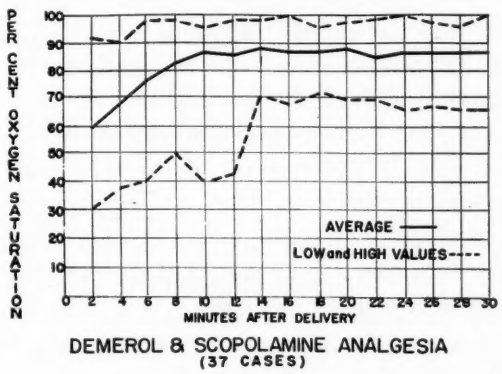

Fig. 2.—Oxygen saturation studies performed on normal newborn infants whose mothers received Demerol and scopolamine analgesia but no general anesthesia (37 cases).

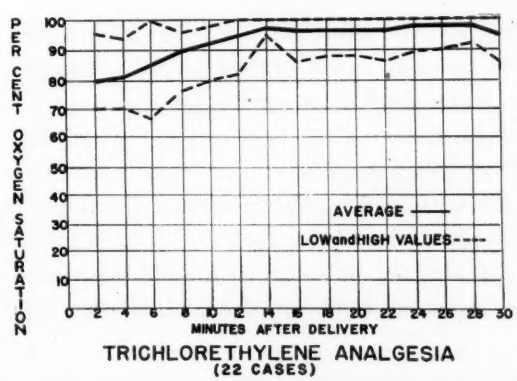

Fig. 3.—Oxygen saturation values during the first half hour of life in normal newborn infants whose mothers received trichlorethylene analgesia (22 cases).

The 37 infants whose mothers received 100 mg. of Demerol before delivery showed a depression of arterial oxygen saturation values. The average saturation at birth was 59 per cent. The lowest was 30 and the highest was 92 per cent. Fig. 2 shows the oxygen saturation curve for the group throughout the thirty-minute period. After six minutes of life the level of oxygen saturation averaged 76 per cent, and thereafter for the next half hour gradually rose to 87 per cent. The average curve for oxygen saturation in the first half hour after delivery in the Demerol and scopolamine group was significantly lower than the curve of the control group of infants.*

Trichlorethylene series is essentially the same as the control series. It appears that trichlorethylene analgesia has no adverse effects on the neonatal oxygenation of the blood of a full-term normal newborn infant (see Fig. 3).

Comment

Demerol is widely used and has general professional acceptance as an analgesic drug of a relatively high degree of usefulness and safety. Although Demerol has proved to be a safe drug through clinical experience it does produce some mild depression of arterial oxygen saturation in the baby during the early neonatal period. Its combination with other general anesthetic agents does produce some measurable and clinical hypoxia.[2]

Trichlorethylene has had a long clinical trial in England and Canada and has wide acceptance in these countries as a safe obstetrical analgesic.[5-10] Many obstetricians in this country have used the agent for relief of pain during the late first stage of labor, the second stage, and for delivery itself.[11-14] We have used trichlorethylene analgesia over the past three and one-half years and feel that it is of value and safe for both mother and child. We are careful to limit its use to analgesic purposes. The patient is the only one permitted to administer trichlorethylene to herself.

There have been reports on the induction of cardiac irregularities in the mother with trichlorethylene; none have been serious.[11, 15, 16] Uniform findings regarding the absence of respiratory depression in adults have been reported. Some authors have emphasized the importance of not using trichlorethylene in a closed-circuit anesthesia system. Trichlorethylene, when passed through soda-lime and heat, may be broken down into the poisonous gas phosgene (carbonyl chloride) and hydrochloric acid.[10, 15]

Our experiments in the measurement of arterial oxygen saturation with the use of oximeter have demonstrated higher levels of oxygen saturation than when we use chemical methods for measuring the amount of oxygen in the blood of the newborn infants.[1, 2] This does not reflect inaccuracies for either method. It is a general observation that the head and the ears of a normal newborn baby become pink and oxygenated almost immediately after delivery in the uncomplicated cases, whereas the feet and hands may remain in a relative state of cyanosis for several minutes to a half hour after delivery. Our chemical measurements had been performed on capillary blood taken from the heel of the child.

*According to the "t" test, ten of the differences between the means are significant beyond the 1 per cent level of confidence, and five between the 1 per cent and 5 per cent level of confidence. The statistical analysis was performed by Dr. Edith Boyd and Mrs. Susan Lee.

Conclusions

1. Demerol and scopolamine given in normal and safe amounts to the mother in labor may cause some measurable and statistically significant depression of normal blood oxygenation of the newborn infant.

2. Trichlorethylene, when self-administered by the patient for analgesia in labor and delivery, has no effect on blood oxygen levels of the child at birth, or during the first half hour of life.

Summary

A double-scale, absolute-reading, alternating-current oximeter with an infant-sized earpiece was used to measure the per cent oxygen saturation in the blood of normal newborn infants during the first thirty minutes of life. Determinations were made every two minutes. The effect of Demerol and scopolamine was measured and it was found that this combination of drugs did produce measurable and significant depressions in blood oxygen saturation of the normal full-term newborn infant. The depressed blood oxygen levels were not injurious or pathologic in this series, however. A similar experiment designed to check the analgesic agent, trichlorethylene, showed it to have no measurable effect on the blood oxygen saturation of the infants studied.

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THE ACTION OF TRICHLORETHYLENE ON THE CARDIOVASCULAR SYSTEM

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THE central depressing effect of trichlorethylene suggested its use in the alleviation of pain both as a narcotic and as an analgesic agent. Trichlorethylene has been employed as a narcotic in the treatment of trigeminal neuralgia,[1, 2, 3, 4] migraine,[5, 6] and angina pectoris,[7, 8] but continued successes have been reported only in its use as an analgesic agent in obstetrics.

There has been about ten years of satisfactory experience with trichlorethylene as an analgesic agent in obstetrics, and the British, who were the first to become interested in it for this purpose, were probably stimulated by the report of Freeman[9] in 1943. Using a suitable inhaler, he employed trichlorethylene mixed with air and found that it was satisfactory even for mothers afflicted with toxemia or rheumatic heart disease and that infants were unaffected. Calvert[10] thought that his experience was encouraging for a painless delivery. Reporting for the Royal College of Obstetrics and Gynaecology in 1949, Reynolds,[11] however, warned that it should not be made available to "unsupervised domiciliary midwives." Favorable reports, nevertheless, continued. Hewer[12] thought that trichlorethylene could replace chloroform, since in his experience it was less toxic to the liver and less likely to cause cardiac failure. Seward[13] employed 0.5 per cent trichlorethylene in air for self-administered analgesia and found that it was more effective than the nitrous oxide-air mixture in relieving the pain of uterine contractions, but preferred it to the latter only for fast-moving labor and nervous patients. He did not think it suitable for prolonged administration. Scales and Ohlke[14] recommended trichlorethylene for both obstetrical analgesia and anesthesia because it was safe and efficient, produced few side effects, was readily received by the parturient patient, and was relatively inexpensive since it was needed only in small quantities. Browne and McCormick[15] suggested further trial on the basis that trichlorethylene was capable of giving an amount of relief comparable to that given by nitrous oxide and air, but found that it was less agreeable to inhale than gas and that uterine tone diminished after long periods of use or with high concentrations. Palliez and associates[16] studied trichlorethylene clinically and biologically. These workers found that it could be employed with ease, that it was of real value as an analgesic agent for the pain of labor, and that it possessed no untoward action on the progress of labor. They thought that the apparent absence of toxicity to the

infant could be explained by the fact that trichlorethylene was found in higher concentrations in the mother's blood than in fetal blood. Their research obliged them, however, to suggest that trichlorethylene be used with caution. In 1953, enthusiastic articles were published by Smith,[17] Sergent,[18] Albert,[19] Flowers,[20] and Rawlings,[21] but an editorial,[22] conservative in tone, weighing the enthusiasm of Rawlings and the caution of Seward, was written in the *British Medical Journal.* Rawlings suggested that trichlorethylene might even be employed by midwives after the cervix had dilated to three fingerbreadths, with the proviso that analgesia would be stopped: (1) if labor was not completed in six hours, and (2) if uterine contractions decreased in strength and frequency.

Among these reports, one can find little or no reference to the cardiovascular effects of trichlorethylene. A complete study of these possible effects has not been reported, and only a few studies have been devoted entirely to any of them. Krantz and associates[23, 24] concluded that "the drug produces hypoalgesia by depressing the basal ganglions and possibly causes a relaxation of the vessels of the splanchnic area while producing peripheral vasoconstriction." Barnes and Ives[25] observed multifocal ventricular tachycardia with the electrocardiograph during trichlorethylene anesthesia and thought that this constituted a potential danger, particularly if Adrenalin was also used. It was also concluded that trichlorethylene should not be used routinely with gas and oxygen. Ewing and Brittan[26] observed auricular fibrillation following trichlorethylene anesthesia. Hilliwell and Hutton[27] reported that despite gross overdosage to the mother, electrocardiograms of fetal sheep did not show prolonged P-R intervals, bradycardia, or other arrhythmias, and trichlorethylene appeared in the fetal circulation in higher concentration than in the maternal. Noble and Cattanach[28] thought that their results with trichlorethylene analgesia improved with experience, but reported the occurrence of bradycardia, tachycardia, and extrasystoles.

Since the benefits reported from the use of trichlorethylene in migraine and angina pectoris may be due to vascular and cardiac effects as well as a central depressing effect, and since during its use as an analgesic agent in labor the cardiovascular effects of the drug may be important, an extensive investigation of the possible cardiovascular effects of trichlorethylene should be of interest.

Experimental

Action on the Heart.—

The object of these studies was to determine the action of trichlorethylene on the myocardium and on the conducting system of the heart. Lever experiments on the frog's heart and electrocardiographic experiments on human, canine, and rabbit subjects were performed.

Preliminary lever experiments on the frog's heart indicated that the character of the beat changed after trichlorethylene had been dropped on the surface of the heart. Such experiments were repeated in ten frogs. The results were alike and are illustrated in Fig. 1. This kymogram shows the effect of 1 c.c. of trichlorethylene (dropped slowly on the heart from a syringe) and

of subsequent washing with physiologic saline. The auricular tracing is at the top, the ventricular at the bottom. Time in five seconds and points of change are indicated in the center. Section A to B is the control record, B to C after 1 c.c. of the drug was used, and C to D after washing with saline. The effect of the drug is immediate: the rate is slowed, the notching seen in the control disappears, and the amplitude of the auricular contraction is affected to a greater extent than that of the ventricle. When the heart is washed with physiologic saline, the effects of trichlorethylene are removed. If more than 1 c.c. of the drug is used, the heart continues to slow and stops in about five minutes. Washing with physiologic saline does not then revive the heart.

Electrocardiographic studies have been reported elsewhere but a summary is included for completeness.[29] Human, canine, and rabbit subjects were employed. The effects revealed by the canine and rabbit experiments include marked slowing of heart rate, ectopic beats, and alterations in the P and T waves. The conducting mechanism and the myocardium are affected. Fig. 2 illustrates the effects of increasing amounts of trichlorethylene on the electrocardiogram of a dog. *A* is the control record; *B* is the record after 5 c.c. of trichlorethylene by inhalation; *C*, after 1 c.c. intravenously; *D*, after 3 c.c. intravenously; *E*, *F*, and *G*, after the sixth, seventh, and eighth cubic centimeters of the drug had been injected; and *H*, as the dog died.

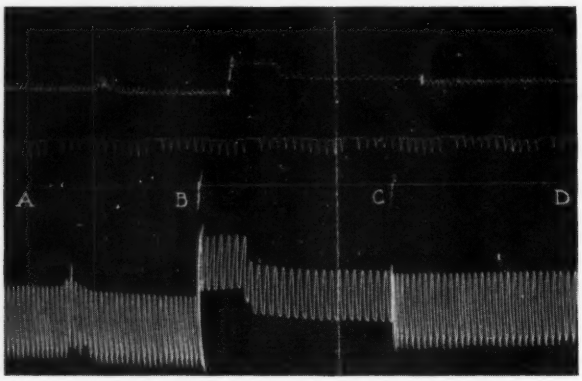

Fig. 1.

The administration of the therapeutic dose of 1.0 c.c. of trichlorethylene does not produce significant electrocardiographic changes either in human subjects afflicted with cardiovascular disorders or in normal subjects.

Action on Blood Pressure.—

Human subjects were employed to study the effects of the therapeutic dose of trichlorethylene on blood pressure. The results of this study have also been reported.[29] It was concluded that the therapeutic dose of trichlorethylene does not produce significant blood pressure changes either in human subjects afflicted with cardiovascular disorders or in normal subjects.

Dogs were employed to determine the effects of large amounts of trichlorethylene on the blood pressure and respiration; the kidney volumes were also recorded. Eight dogs were used that weighed from 35 to 40 pounds. Anesthesia was accomplished with Nembutal. Trichlorethylene was given by inhalation and intravenously. Figs. 3 to 8, inclusive, illustrate the results obtained.

In Fig. 3 the blood pressure tracing is labeled *B*. The experiment in which this record was obtained consisted of permitting the dog to breathe trichlorethylene for two minutes from a piece of gauze in which an ampule of the drug (containing 1 c.c.) was broken. A rise in blood pressure occurred, but at its height the rise was only about 10 mm. Hg and its duration about 4 minutes. The blood pressure tracing in Fig. 4 labeled *E* was obtained in an experiment similar to the one described in Fig. 3. In this instance, one out of ten experiments, a shallow drop in blood pressure occurred when trichlorethylene was inhaled. When the inhalation was discontinued, however, the drop was followed by a rise, equal to that which may be seen in Fig. 3. It is clear that a small rise in blood pressure was the more constant finding in the inhalation experiments, with the use of a small quantity of trichlorethylene.

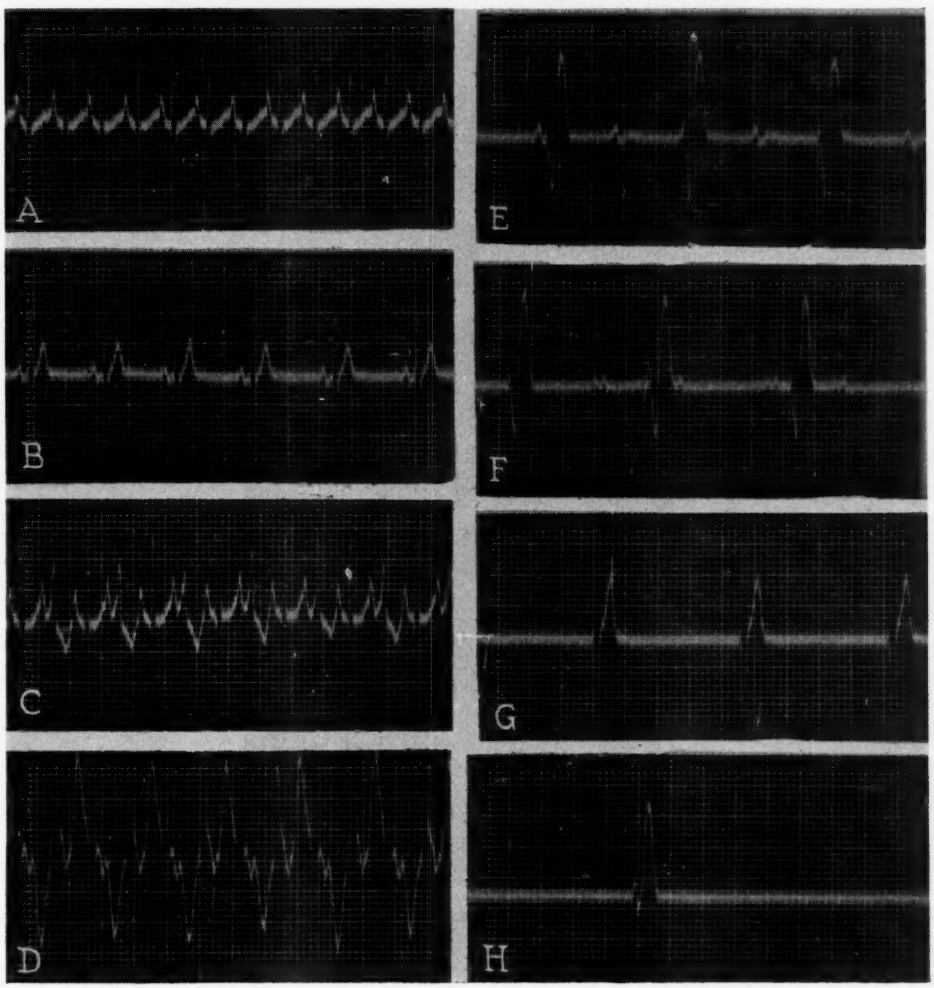

Fig. 2.

Trichlorethylene was injected into a dependent portion of the trachea of a dog in the experiment depicted in Fig. 5. The object, here, was to give a large amount of the drug by inhalation. The blood pressure tracing is marked *D* in this figure. The immediate effect of the injection was to stop the beat of the heart. This lasted for about 10 seconds, during which time the blood pressure first dropped and then rose. Even after the heart resumed beating,

however, the blood pressure continued to decline. The lowest point in the drop, about 20 mm. Hg, was reached in about a minute and a half, while the entire phase lasted about 5 minutes.

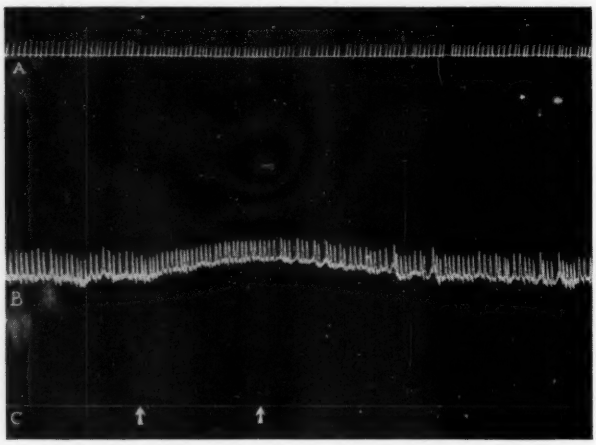

Fig. 3.

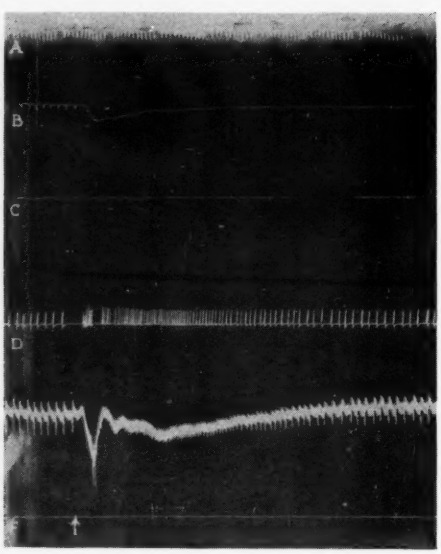

Fig. 4.

Trichlorethylene was rapidly injected intravenously in the experiments presented in Figs. 6, 7, and 8. In Fig. 6, 0.5 c.c. was injected, in Fig. 7, 1 c.c. was injected, and in Fig. 8, 1 c.c. was injected after the vagi had been cut and the blood pressure had leveled off. The blood pressure tracings are labeled *E* in each of these figures. The blood pressure immediately dropped in each instance. When 0.5 c.c. of the drug was injected intravenously, however, the blood pressure did not remain low as long as when 1 c.c. was used, nor was the drop as great. When 1 c.c. of trichlorethylene was injected intravenously after the vagi had been cut, the blood pressure tracing simulated that seen when 1 c.c. of the drug was injected into the trachea.

Action on Respiration.—

In the experiments shown in Figs. 3 and 4, in which 1 c.c. of trichlorethylene was inhaled over a period of two minutes, the respiration tracings are labeled *A* and *D*, respectively. In these experiments, a small increase in

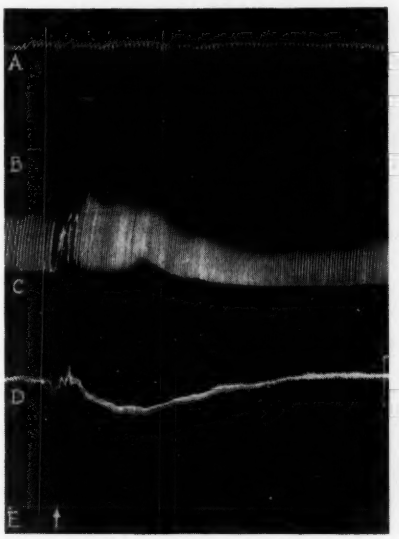

Fig. 5.

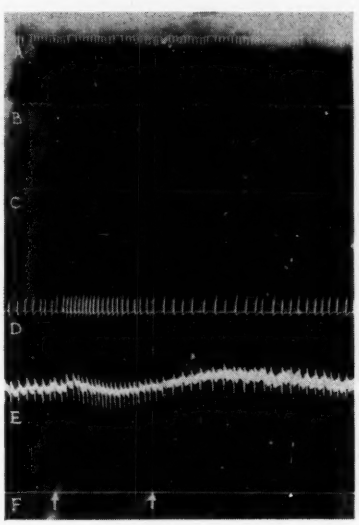

Fig. 6.

the rate may be observed. When 1 c.c. of trichlorethylene was injected into the trachea, as shown in Fig. 5, the respiration (labeled *C*) first stopped and after about 10 seconds continued very rapidly until the blood pressure returned to normal. This description applies also to the experiments illustrated in Figs. 6 and 7, in which 0.5 c.c. and 1 c.c. of the drug were rapidly injected intravenously. In these figures, the respiration tracings are labeled *D*. In the experiments in which the vagi had been cut before 1 c.c. of trichlorethylene was injected intravenously, respiration did not stop when the drug was given.

Only an increase in rate occurred, lasting, as in the other experiments, until the blood pressure returned to its preinjection level.

The effect of the therapeutic dose of trichlorethylene (1.0 c.c.) on respiration was tested on human beings, 6 normal subjects and 10 subjects afflicted with cardiovascular disturbances being employed. No subject experienced any serious respiratory difficulty. Only 3 subjects experienced dizziness, and only 2 (both with cardiovascular disease) experienced some choking.

The effect of trichlorethylene on respiration was also observed in rabbits. In these tests the anesthetic dose was administered. The animals were first placed in a basal state,[30] and then given the anesthetic by way of a small ether mask. Two rabbits were anesthetized every day for a week, while two others were anesthetized every day for a month. Though the main purposes of these repeated anesthetizations were to produce possible pathologic and electrocardiographic changes, it was also possible to observe the changes in respiration characteristic of the different stages of anesthesia. In general, it may be said that these changes were similar to those observed when any of the other gas anesthetics were administered, e.g., ether, chloroform, etc. It is of interest that only 2 c.c. of trichlorethylene was required to produce complete anesthesia in rabbits that weighed from 5 to 6 pounds.

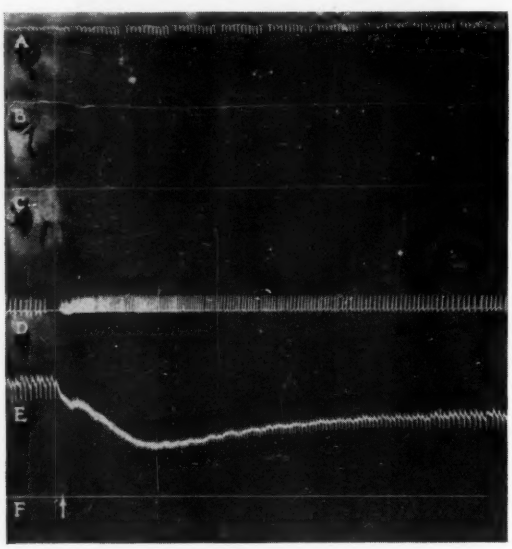

Fig. 7.

Action on Circulation.—

The effect of the administration of trichlorethylene on circulation was tested in three ways: possible changes in kidney volume, capillary dimension, and coronary flow.

Kidney-volume studies were carried out on dogs and are included in the kymograms presented in Figs. 4, 6, 7, and 8. In these figures the kidney-volume tracings are marked *B*. Only a small drop in kidney volume took place in the experiment illustrated in Fig. 4, in which trichlorethylene was inhaled. In Figs. 6 and 7, experiments dealing with the intravenous injection of 0.5 c.c. and 1 c.c. of trichlorethylene, relatively significant drops in kidney volume resulted. These volume drops simultaneously followed the fall in blood pressure which also occurred. From Fig. 8, picturing an experiment which dealt

with the intravenous injection of trichlorethylene after the vagi had been cut, it will be seen that the change in kidney volume was small, not unlike that when the drug was inhaled.

The effect of trichlorethylene on capillaries was studied in human subjects and frogs. They were visualized with a capillary microscope and measured with a micrometer. The capillaries of the parietal peritoneum were visualized in the case of the frogs, while those of the nail bed of the ring finger of the left hand were observed in the human experiments. Capillary loops were brought into focus in all instances in order to study both the arterial and venous divisions. The therapeutic dose of trichlorethylene was inhaled by the human subjects, while a piece of cotton moistened with the drug was placed in the buccal cavity of the frogs.

In a series of 10 frog experiments, constriction of the arterial side of the capillary loop was observed in every instance. The dimension of the arterial division was approximately 50 per cent smaller after the drug was administered. Return to the original size occurred in about ten minutes. The venous portion of the loop remained unaffected.

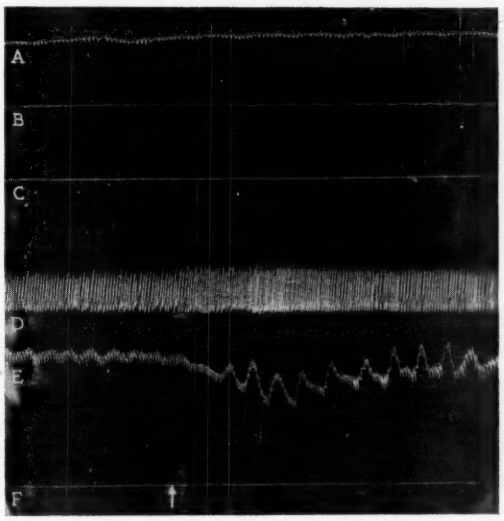

Fig. 8.

The tests carried out on the 13 different human subjects (Table I) also indicated that the arterial sides of the capillary loops were affected and that the venous sides were unaffected. The degree of constriction of the arterial side of the loops in these tests was approximately the same as in the frog experiments—50 per cent. Return to the original size, however, did not take place before 20 minutes.

In a series of tests on three human subjects, 1.0 c.c. of trichlorethylene was inhaled on 8 succeeding days, and their capillaries were studied after each inhalation to note variation of the effect in a single individual (Table II). Constriction of the arterial portion of the capillary loops always occurred. In these subjects, deep breathing by itself never produced the degree of change observed after trichlorethylene was inhaled.

What effect trichlorethylene might have on coronary flow was studied with the Rhein thermostromuhr. Experiments were carried out on 12 dogs that weighed from 35 to 40 pounds. The animals were anesthetized with Nembutal. In the first portion of these experiments 1 c.c. of trichlorethylene was

inhaled for five minutes from a square of gauze in which an ampule of the drug was crushed. In the next part, 1 c.c. of the drug was injected quickly into a dependent portion of the trachea. In the last part, 1 c.c. of the drug was injected quickly into a femoral vein. Control and test readings are presented in Table III. Test readings were taken at 1, 2, 3, 4, 5, 10, 15, and 30 minutes after the administration of the drug.

TABLE I. CAPILLARY DIMENSIONS* OF DIFFERENT HUMAN SUBJECTS BEFORE AND AFTER INHALING TRICHLORETHYLENE

SUBJECT	BRANCH†	BEFORE	AFTER‡
S. C. W.	a	10	0
	v	20	0
O. D. B.	a	20	10
	v	20	20
J. R. C.	a	20	10
	v	20	20
E. B. L.	a	20	10
	v	25	25
H. S.	a	10	0
	v	20	0
G. M.	a	15	10
	v	25	25
J. M.	a	10	0
	v	15	0
M. B.	a	10	10§
	v	15	15
J. N.	a	15	10
	v	20	20
E. Z.	a	10	10§
	v	15	15
V. J.	a	10	10§
	v	20	20
E. M.	a	15	10
	v	20	20
A. B.	a	10	10§
	v	20	20

*In microns.
†a, Arterial; v, venous.
‡Before and after trichlorethylene.
§Less than 10 μ.

TABLE II. CAPILLARY DIMENSIONS* OF HUMAN SUBJECTS GIVEN TRICHLORETHYLENE ON EIGHT SUCCESSIVE DAYS

		DAYS													
		1		2		3		4		5		6		7		8	
SUBJECT	BRANCH†	B‡	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A
G. L.	a	10	X	10	X	10	0	10	0	10	X	15	X	10	X	15	X
	v	20	20	20	20	20	0	20	0	20	20	20	20	20	20	20	20
J. N.	a	15	10	15	X	10	X	15	X	10	0	15	X	15	10	10	X
	v	20	20	20	20	15	20	20	20	20	0	20	20	25	25	15	20
S. W.	a	10	X	10	0	10	X	10	X	10	0	10	X	10	X	10	0
	v	15	20	15	0	15	15	15	15	20	0	20	20	15	15	20	0

*In microns.
†a, Arterial; v, venous.
‡B, before, and A, after trichlorethylene.
X, Less than 10 μ.
O, Capillary faintly outlined.

The coronary-flow readings obtained after trichlorethylene had been inhaled for five minutes did not differ much from the controls. No significant change was observed. When the drug was injected into the trachea, three changes were observed. The first change was a small rise which occurred

immediately after the injection of the drug and lasted about a minute. The second change followed closely and consisted of a moderate drop from the control value, lasting 2 to 3 minutes. The third change overlapped the second and consisted of a gradual rise and return to a rate close to the control value. A considerable drop in coronary flow resulted immediately after the intravenous injection of trichlorethylene, lasting approximately 4 to 6 minutes. Return to a value approaching that of the control did not occur until after about ten minutes.

TABLE III. CORONARY-FLOW READINGS BEFORE AND AFTER ADMINISTRATION OF TRICHLORETHYLENE

	CORONARY FLOW IN CUBIC CENTIMETERS PER MINUTE								
EXP.	CONTROL	1*	2	3	4	5	10	15	30
1 c.c. Trichlorethylene Inhaled From a Square of Gauze.—									
1	40	45	40	40	40	35	35	30	30
2	50	50	50	50	45	45	40	40	35
3	40	50	45	45	40	40	40	40	35
4	45	40	40	40	35	35	35	35	30
1 c.c. Trichlorethylene Introduced Into Trachea.—									
1	50	60	45	40	50	55	55	45	40
2	55	70	50	40	40	40	45	40	45
3	45	55	30	35	30	35	40	40	30
4	50	65	35	30	35	45	45	45	45
1 c.c. Trichlorethylene Injected Intravenously.—									
1	45	10	10	10	20	20	30	35	40
2	60	15	10	10	10	30	40	45	45
3	55	10	10	20	30	40	50	50	35
4	50	10	10	30	40	40	45	40	30

*Minutes after administration of trichlorethylene.

Summary and Comment

Lever experiments on the frog's heart and electrocardiographic experiments on human, canine, and rabbit subjects were performed to study the effect of trichlorethylene on the heart. In the lever experiments on the frog's heart, the kymograms show immediate effects. These effects include a slowing in rate, disappearance of the dicrotic notch, and reduction of amplitude of both the auricular and ventricular beats. When large quantities of the drug were used, the heart stopped. It may be concluded here that trichlorethylene is toxic to the frog's heart, affecting the myocardium and the conducting mechanism. Since the administration of small amounts of trichlorethylene to human subjects does not produce electrocardiographic changes, it may be concluded that this quantity in itself is not harmful to the human heart. Nevertheless, since the administration of large quantities of trichlorethylene to dogs and rabbits, or repeated use, produces alterations in rate and rhythm, and changes in the P and T waves, it may be supposed that such administration in comparable doses might produce similar effects in the human being.

The effect of small quantities of trichlorethylene on blood pressure, as observed in human subjects, is negligible. No significant changes were observed. On the other hand, the blood pressure changes observed in dogs from comparably large quantities of trichlorethylene are considerable. Similar blood pressure changes, therefore, also might be possible in human subjects if comparable doses were used. The primary effect of the drug on blood pressure

is depression, as seen when it is injected intravenously. When it is inhaled from a square of gauze or after introduction into a dependent portion of the trachea, however, a small rise in blood pressure is produced, which is short in duration and lasts only about a half minute. This phase is quickly followed by depression, which lasts longer. The small rise in blood pressure observed in the first phase of an inhalation experiment is very likely produced reflexly by chemical irritation of the mucous membrane of the respiratory tract. The reason the depression in blood pressure in the second phase of an inhalation experiment is not as great when trichlorethylene is inhaled from a square of gauze as when introduced into the trachea is that a sufficient concentration in the blood stream cannot be obtained in this manner. To obtain a blood concentration sufficient to depress the blood pressure, a comparatively large amount of the drug must be inhaled rapidly or injected intravenously. The fact that a depression in blood pressure is produced upon the intravenous injection of trichlorethylene and after the vagi are severed may indicate that the mechanism is other than stimulation of the parasympathetic nerves. For example, splanchnic dilation can be the cause.

The changes in blood pressure just summarized may be used to explain the observed alterations in respiration, kidney volume, capillary size, and coronary flow.

Increase in rate is the primary effect of trichlorethylene on respiration and as suggested is probably associated with the concomitant blood pressure depression. When the blood concentration is quickly increased, as after the introduction of a comparatively large amount of the drug into the trachea or after intravenous injection, the respiratory center is probably temporarily shocked, which can explain the temporary stoppage of respiration observed in these instances. A vagal reflex can also explain the stoppage, for it was not observed when the vagi were cut. On the other hand, if anesthesia is desired and trichlorethylene is administered from an apparatus like an ether mask, sufficient concentration in the blood stream is obtained slowly. During such a procedure the respiratory changes are similar to those observed when any gas anesthetic is administered. Any respiratory changes which can be caused in human subjects by the administration of small quantities of the drug are probably produced reflexly, from irritation of the mucous membrane of the respiratory tract.

The significant drop in kidney volume observed on the injection of trichlorethylene intravenously is probably due to the simultaneous considerable drop in blood pressure produced. This conclusion is substantiated by the fact that when the blood pressure drop is not large, reduction in kidney volume is very small or does not occur.

The constriction of the arterial side of the capillary loops, observed both in the human and frog experiments, is very likely compensatory to splanchnic dilation.

Alterations in coronary flow observed after the administration of trichlorethylene could also be related to blood pressure changes. No direct action of

the drug on the coronary arteries was discerned. When trichlorethylene is administered by inhalation from a square of gauze, coronary flow does not significantly change from control values. Under these conditions blood pressure similarly does not vary to any considerable extent from the preadministration value. When trichlorethylene is introduced into the trachea, however, the three changes which take place follow closely in time the changes in blood pressure. The increase in flow observed initially occurs simultaneously with the initial increase in blood pressure. This phase is of short duration and is followed immediately by a decrease in flow which occurs concomitant with the blood pressure depression. The last phase consists of a slow return to approximately the control value. Here, also, the blood pressure slowly rises to approximately its control value. In the tests where trichlorethylene is injected intravenously, the coronary flow and blood pressure findings are similar, except that an initial rise is not observed, and the drops are greater. The large drops observed are probably due to the overwhelming blood concentration and to the absence of reflex effect by irritation. Although blood pressure changes can be utilized to explain the differences in coronary flow produced by the administration of trichlorethylene, other effects such as cardiac rate and action also may exert an influence.

The results of our studies may be used to warn against the employment of trichlorethylene for cardiac effect. Dangers are revealed by the results of practically all of the experiments in which little more than the therapeutic dose of the drug was used. Since trichlorethylene can produce rather severe changes in cardiac rate and action in animals, in quantities little above the so-called therapeutic dose, it may be well to point out the possibility of similar effects on the human heart by comparable amounts of the drug. Despite the possible safety of the small therapeutic dose, 1.0 c.c., relatively large amounts of the drug could be administered when the drug is employed as an analgesic agent during labor. Under such circumstances, in the light of our experiments, untoward cardiovascular effects would not be surprising and thus caution, at least, might be deemed necessary.

Conclusions

Trichlorethylene affects both the myocardium and conducting mechanism of the heart, when used repeatedly or in comparatively large amounts. The administration by inhalation of a single therapeutic dose, 1.0 c.c. of the drug, however, is not harmful to the human heart.

The primary effect of trichlorethylene on blood pressure is depression, and the probable mechanism is splanchnic dilation.

The effects on respiration, kidney volume, capillary size, and coronary flow are probably due to multiple causes such as blood pressure, heart rate, and rhythm. Respiration rate is increased, volume is lowered, capillary constriction occurs, coronary flow decreases, and irregularities in rate and rhythm are observed.

The benefits reported from the use of trichlorethylene in angina pectoris are not supported by this investigation. If migraine is due to caplliary vaso-

dilation, then the action of the drug on capillaries can explain the benefits reported in this condition. Since there is considerable danger in the concomitant blood pressure depression, any value obtained from its action on capillaries is overbalanced.

Since comparatively large amounts of trichlorethylene may be administered when it is employed as an analgesic agent during labor, it may be well to warn that untoward cardiovascular effects may occur.

This study was begun while the senior author was a member of the Department of Medicine at Northwestern University School of Medicine. He wishes to thank Dr. A. Luisada, Coordinator of Cardiology, Department of Medicine, and Dr. S. Contro of the same Department, Chicago Medical School, for their interest and suggestions.

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FURTHER OBSERVATIONS ON LIVING HUMAN OOCYTES AND OVA

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STUDIES in 1953[1, 2] were concerned with methods for securing and investigating living follicular and tubal human ova by means of phase contrast microscopy, a procedure for obtaining their complete denudation, spermatozoan behavior about and penetration of the ovum, the constituents of the zona pellucida and the perivitelline space, and maturation stages with special reference to polar body formation. The work has been extended in an effort to obtain additional information about early development in the human female germ cell.

Materials and Methods

Living human oocytes and tubal ova were again used in the present studies. They were investigated by means of phase contrast microscopy in the same manner as in the previous publications.[1, 2]

Results

Follicular Stages.—Even though the oocyte upon removal from the follicle is normally surrounded by the corona radiata and some cumulus cells, at times the outline of the nucleus can be discerned in varying degrees. If slight pressure is made upon the cover glass, which is supported by a ring of petrolatum, so as to flatten the cell somewhat, the nucleus is often very clearly observed as shown in Figs. 1 to 8.

During part of its existence the human oocyte contains the yolk-nucleus, a small spheroidal body within a crescent-shaped pallial layer (Fig. 2). According to Wilson,[3] the pallial layer is found only in the earlier stages of the oocytes and does not long persist as such in lower animals. He believed that it consists largely of chondriosomes as well as Golgi bodies and also nucleolar material and that the yolk-nucleus-pallial layer complex shows a close analogy to the idiosome complex of the spermatocytes, and that the two may be regarded as homologous formations. This observation for living human ova has not previously been reported.

When seen, the nucleus was noted invariably to be round and eccentric in the ooplasm. When focused upon in the equatorial plane, the nuclear membrane or limiting boundary was uniform in thickness (Figs. 3, 5). In the nuclei shown in Figs. 7 and 8 the chromosomal material is believed to be in the stage of tetrad formation.

*Markle Scholar in Medical Science.

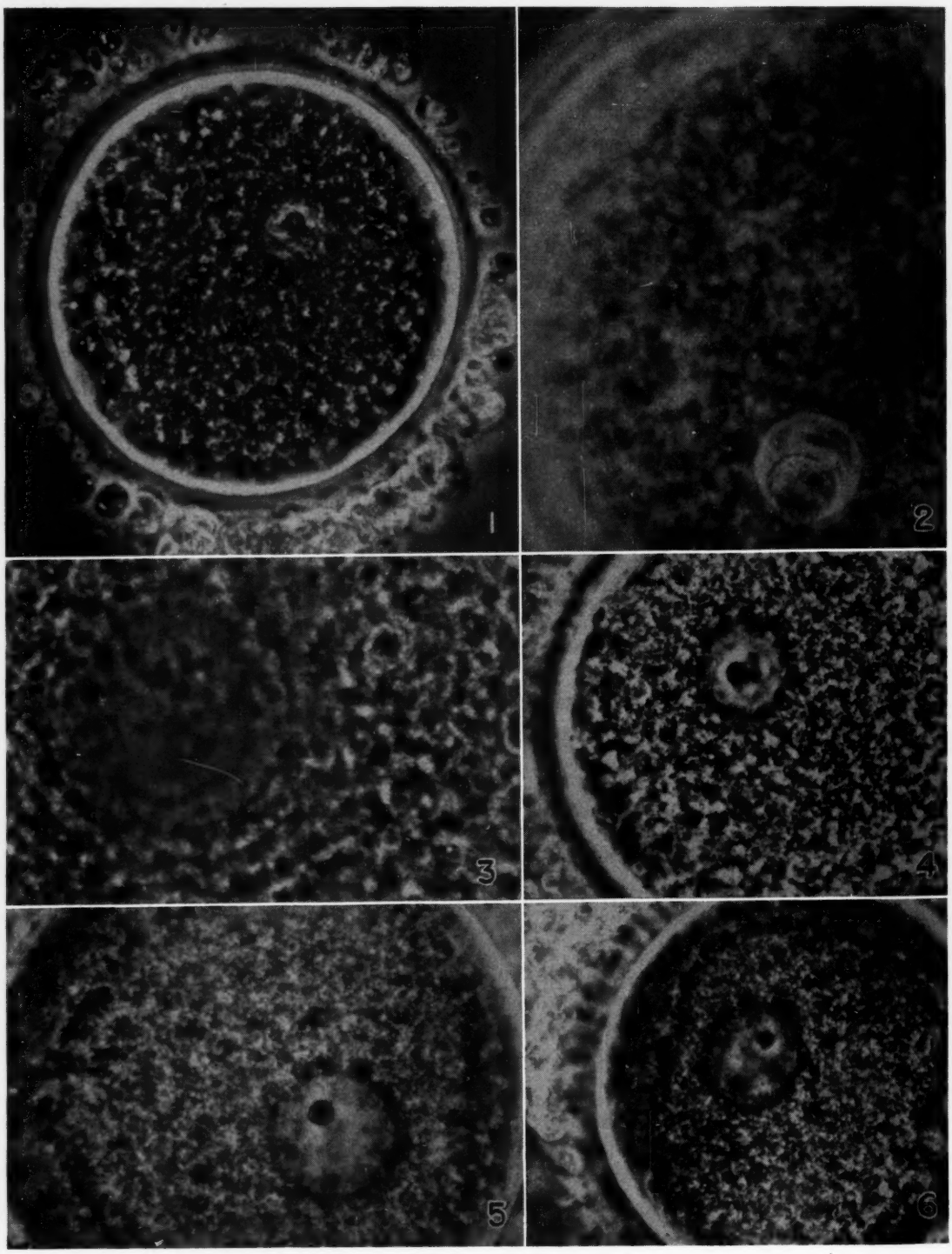

Fig. 1.—Primary oocyte. (×100; all reduced ⅓.)
Fig. 2.—Yolk-nucleus-pallial layer complex in primary oocyte. (×200.)
Fig. 3.—Nuclear membrane or limiting boundary in primary oocyte. (×430.)
Fig. 4.—Primary oocyte. (×100.)
Fig. 5.—Primary oocyte. (×100.)
Fig. 6.—Primary oocyte. (×100.)

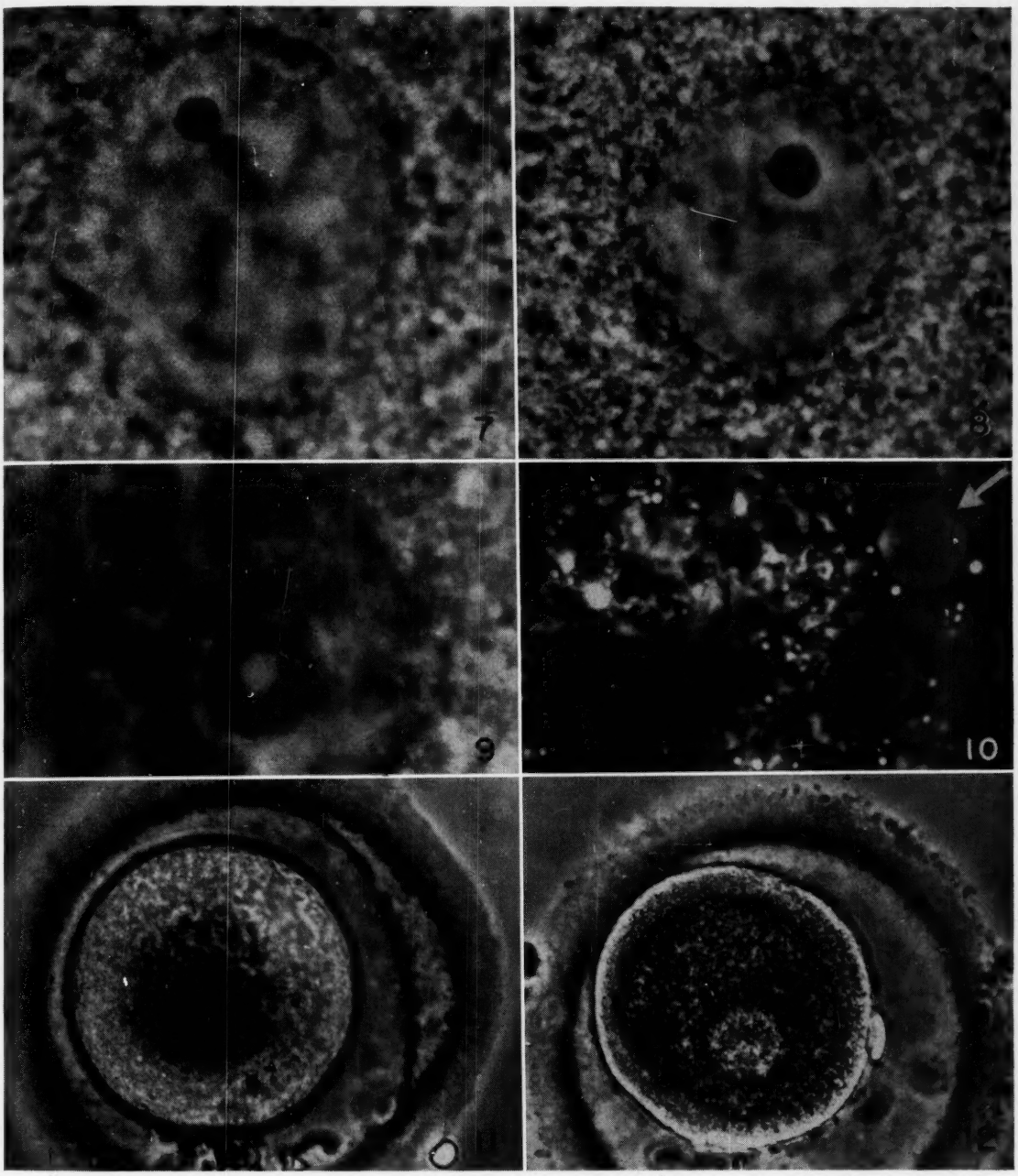

Fig. 7.—Nucleus, chromosomes in tetrad formation and eccentric nucleolus in primary oocyte. (×430; all reduced ⅓.)

Fig. 8.—Nucleus, chromosomal material and eccentric nucleolus in primary oocyte. (×430.)

Fig. 9.—Nucleolus in primary oocyte. (×970.)

Fig. 10.—Intact nucleolus, dissected free. (×970.)

Fig. 11.—Zona pellucida partially freed from perivitelline contents in primary oocyte. (×200.)

Fig. 12.—Secondary oocyte almost formed. (×200.)

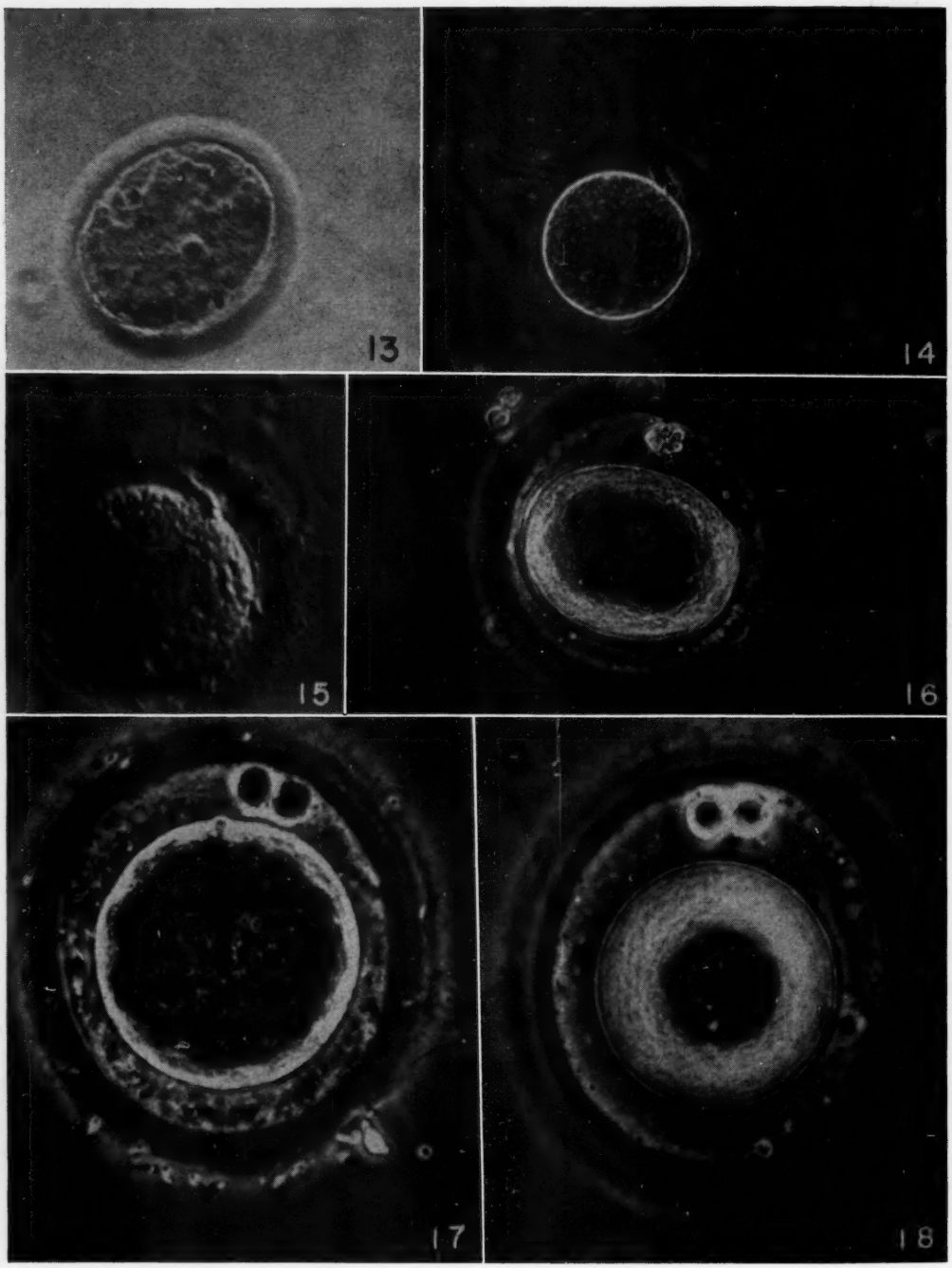

Fig. 13.—Ovum after approximately 24 hours in the Fallopian tube. (×100; all reduced ⅓.)
Fig. 14.—Recently denuded tubal ovum. (×100.)
Fig. 15.—Same ovum as shown in Fig. 14, different view. (×100.)
Fig. 16.—Tubal ovum with early degeneration of first polar body. (×100.)
Fig. 17.—Division of first polar body, spermatozoa in zona pellucida, tubal ovum. (×100.)
Fig. 18.—Division of first polar body, tubal ovum. (×100.)

When observed, there was a single nucleolus. It was eccentric within the nucleus, and in so far as could be ascertained, was homogeneous in consistency and almost round (Figs. 1, 4 to 10). When dissected free, the nucleolus remained intact as depicted in Fig. 10.

The perivitelline space and its contents usually extend to and lie in such close proximity with the inner surface of the zona pellucida that no space is detectable between the two. An oocyte is shown in Fig. 11 in which the zona pellucida was stretched so as to be pulled away from the perivitelline area in part of its circumference. There appears to be a very definite limiting boundary or membrane surrounding the perivitelline contents. This has been seen occasionally in ova without dissection; normally, however, this space is a potential one.

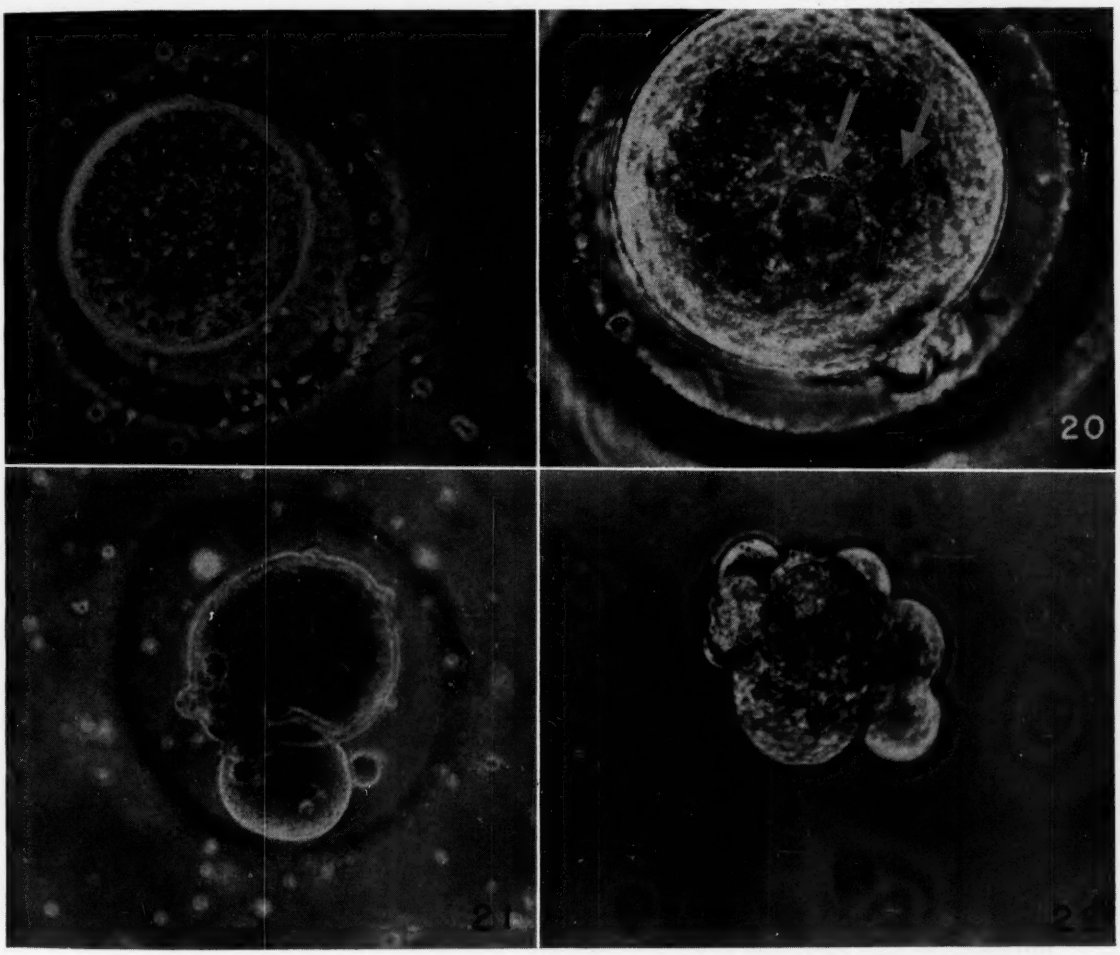

Fig. 19.—Recently denuded tubal egg with spermatozoan penetration. (×100; all reduced ⅓.)

Fig. 20.—Division of first polar body, possible pronuclei outlined in close proximity to each other in tubal ovum. (×200.)

Fig. 21.—Two-cell stage obtained after 30 hours of exposure to spermatozoa in vitro (×100.)

Fig. 22.—Eight-cell stage obtained after approximately 60 hours of exposure to spermatozoa in vitro. (×100.)

An oocyte showing the first polar body being formed and the eccentrically situated germinal vesicle was obtained from a large follicle at about midcycle (Fig. 12). This oocyte is considered to be almost ready for release from the Graafian follicle into the Fallopian tube. The cumulus and corona cells were removed through the enzymatic action of the tubal mucosa in the follicular fluid in vitro, which action will be commented on later.

Tubal Ova.—When the ovum is removed from the Graafian follicle or soon after its entry into the Fallopian tube, the corona radiata and part of the follicular cumulus surround the zona pellucida. Within the tube, complete denudation of these cells occurs. The exact time required for this is not known; Fig. 13, however, is the photograph of an egg obtained approximately 24 hours after ovulation as judged by the time in the menstrual cycle. The first polar body can be seen in relief, darker.

The tubal ova illustrated in Figs. 14, 15, 16, 17, and 18 are younger than the ovum in Fig. 13. The ova in Figs. 17 and 18 show very clearly the first polar body in the process of division, without the presence of the second polar body. The ovum in Fig. 17 had been exposed to spermatozoa in vitro.

Spermatozoan penetration into the zona pellucida and the perivitelline space can be noted in the fairly recently denuded ovum shown in Fig. 19, the first polar body of which is not seen in this view. Another ovum with the first polar body in the process of division was studied (Fig. 20). The head of a spermatozoon can be seen emerging into the perivitelline space through the zona pellucida at approximately 8 o'clock. Possible pronuclei are outlined in close proximity to each other.

After thirty hours of exposure to spermatozoa in vitro in blood serum to which tubal mucosa was added, the two-cell stage shown in Fig. 21 was observed. The difference in size of the two cells is more apparent than real, due to their lying at different focal depths.

A perfect four-cell stage of an ovum which contained three polar bodies was observed after fifty hours of exposure to spermatozoa in vitro under the same conditions. In transfer it stuck in the capillary pipette and two of the cells were so badly damaged that it was not photographed.

Finally, in Fig. 22 is presented an eight-cell stage after approximately sixty hours of exposure to spermatozoa likewise in vitro. One of the cells does not appear at the focal level at which the picture was taken.

Comment

It has been found that homogenized human Fallopian tubal mucosa is fibrinolytic and contains fibrinolysokinase, whereas the follicular fluid usually contains large amounts of antifibrinolysin and also high concentrations of profibrinolysin; the follicular fluid also can be made fibrinolytic through the action of the tubal mucosa.[4] Therefore, it is believed that, in the denudation of the ovum, its penetration and fertilization by the spermatozoon, this fibrinolytic enzyme action of the tubal mucosa plays a very important part.

In certain cases of sterility for which no demonstrable cause has been found, it may be that there is a deficiency of the enzymatic processes which normally occur in the Fallopian tube. The extremely poor results from the Estes operation, for example, may well result from the absence of the tubal enzymatic action upon the egg preceding and/or during fertilization.

A number of inquiries have been received regarding the possibility of transplantation of an ovum into the uterus of an individual with closed Fallopian tubes or from whom the tubes have been removed. It is believed that before fertilization is accomplished, either in vitro or in the uterus, the egg should have the tubal mucosal factor added to its environment.

Summary

1. The nucleus or germinal vesicle in the human oocyte and mature ovum is round, contains a nuclear membrane or limiting boundary of uniform thickness, and is eccentrically located within the cytoplasm.

2. The yolk-nucleus-pallial layer complex has been observed in the primary human oocyte.

3. The nucleolus is eccentric within the nucleus, homogeneous in appearance, and remains intact when set free.

4. The tubal ovum normally undergoes complete denudation in vivo, and this has also been accomplished in vitro. Denudation is considered to be primarily, if not altogether, due to the fibrinolytic enzymatic activity of the tubal mucosa.

5. The first polar body may undergo division before the egg is fertilized or before the second polar body is released.

6. Cleavage in vitro resulted in two-cell, four-cell, and eight-cell stages, respectively.

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THERAPY FOR INTELLECTUAL OBESITY*
or
Common Sense in Reducing Figures

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AS THE title might or might not indicate, the reduction of figures by common-sense methods refers here to the numbers appearing in medical papers. It will not be possible to give detailed advice on how to read the statistics in medical literature; rather, I want to suggest a few key items to look for when reading a statistical medical paper. These key points do not require technical statistical knowledge, but are rather matters of common sense.

Two Keys to Baldpate.—There are two fundamental ideas that underlie nearly all of medical statistics. Once these two ideas are mastered, the technical details make sense. These two notions are: (1) variation, and (2) bias.

Making Heads and Tails.—For a twenty-cent investment you can learn a great deal about the nature of *variation*. Take twenty pennies and perform the following simple experiment. Shake the pennies in a box and count the number of heads that appear. Repeat this, say, 100 times, and keep a record of the number of heads appearing in each shake. The number of heads will, of course, be variable and, although most of the time about ten heads will appear, there will be some trials where a large excess or deficiency of heads will be found. This is the phenomenon that is called *sampling variation*, that is, variation between the results of the trials, or, in statistical terms, the *samples*. In spite of the apparent irregularity of this variation there are some regularities. While I cannot predict the individual results I can predict what will happen in a large number of trials or samples. For example, I predict that if you carry out this experiment you will find that about three-fourths of the trials will show between eight and twelve heads.

The important point to realize is that a series of twenty pennies is in some ways similar to a series of twenty patients. Suppose, for example, that a doctor is studying a severe disease where only 50 per cent of the patients will survive. If we regard "heads" on the penny as a "death," then there is a close analogy between the results on twenty coins and the clinical results. Of course the medical situation is a great deal more complex and many more factors are operating—a point which will be discussed later—but these factors will be *in addition* to the sampling variation. In this sense the coin experiment represents an *ideal* medical experiment.

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*Presented at a meeting of the New York Obstetrical Society, Dec. 8, 1953.

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A Razor.—Now we know that *sampling variation* occurs with both coins and patients, so it is only common sense to set up the following rule—the first logical principle of statistics:

If the results of a study can be explained in terms of sampling variation alone, we should not attribute these results to other factors.

For example, suppose that a doctor has a new treatment for the hypothetical disease where 50 per cent of the patients have previously died. He treats a series of twenty patients and finds that in his series only seven patients died. Should this doctor rush into print proclaiming the virtues of his new treatment? Should he make such statements as "Only 35 per cent of the patients died instead of the usual 50 per cent," or the even more misleading statement, "As a result of the new therapy, mortality was reduced by 30 per cent"?

There is no need to suppose that the new treatment is effective in order to explain the results; sampling variation is enough to explain them. If you carry out the coin experiment you will notice that seven heads is not uncommon. In fact you will probably find that in about one-fourth of your throws you will get seven or fewer heads or, on the other hand, thirteen or more heads.

How much evidence is needed? The standard currently used, and one which I believe is quite appropriate in the medical field, is the "5 per cent level." For the case of a series of 20 where there is a 50-50 chance of heads or tails or of living or dying, this would lead to the rule:

If there are 5 or fewer deaths on the one hand, or 15 or more deaths on the other hand, then we will look for explanations other than sampling variation.

If we use this type of rule we will be led on a wild goose chase at most once in twenty times. The practical benefits of such a standard are, I believe, especially apparent in medicine. In the past, drugs or therapies have been proclaimed with more enthusiasm than evidence. For a while there is a furor and then the negative evidence begins to pile up and eventually the treatment is forgotten and its place taken by some new ninety-day wonder.

Statistical methods for dealing with sampling variations are like the traditional recipe for cooking rabbit stew that begins: "First, catch your rabbit. . . ."

Cues and Clues.—If a medical paper involves diagnoses, it is reasonable to expect that the best current practices should be used. Thus if biopsies can be made to establish the diagnosis one would have doubts about a paper where no biopsies are reported. In much the same way statistical methods for dealing with sampling variation represent best current practice and any "statistical" paper without such methods would be somewhat suspect.

Even if you are no expert on statistics you can usually answer the question: "Did the author take sampling variation into account?" Look for phrases such as "statistically significant," "probability less than .05," "chi-square test," "t-test," "significance test," "confidence interval," etc. Of course such phrases do not necessarily indicate that the statistical analysis is *correct,* but only that it was made (the same thing would be true for biopsies).

Here are some things to look for which might warn you about accepting the author's conclusions: The author calculates percentages in all cases, even for very short series, and does not warn the reader by a footnote, parentheses, or other such device. The author does not say how large the series are for specific calculations (sometimes the author describes a large series at the start of the paper, but when he gets around to his calculations he uses only a part of the series). The author merely presents the numbers and then "explains" them.

It Gets Worse.—Consideration of sampling variation is only the *first* step (a point often overlooked in statistical papers) and in fact it is the *easiest* step. It will clarify things if we go back to the doctor who tried his new treatment on a series of patients. He has taken our criticism to heart and has done an additional series of 20 patients and there are only 14 deaths in the combined series and this *is* statistically significant by the 5 per cent standard (note that the *proportion* of deaths has not changed but the increase in sample size has made this proportion statistically significant).

"Now," says the doctor, "have I proved my point?"

The answer is "No." One hurdle has been cleared, but there is another and more formidable one ahead. The results of his series are not likely to have come about from sampling variation, but this does not mean automatically that the new treatment is responsible. Let us say that the 50 per cent mortality figure represented earlier series reported in the literature. It is very likely that present series and the past series differed not only with respect to treatment, but also with respect to age and sex composition, diagnostic methods, and a long list of other factors. We are interested in comparing the new treatment with the earlier treatment, but these other factors may very well *bias* our comparison.

Usually biases are subtle, but sometimes they are obvious and these make good examples. Suppose that we wanted to compare the ability of two obstetricians and to do this we compared, say, the proportion of cases in which complications occurred in the course of pregnancy. We might find that one obstetrician had a significantly higher proportion of complications in his patients. Does that prove that he is not as good a doctor?

The chances are that it would be the other way around. Suppose one of the doctors had a widespread reputation as a surgeon. Then cases with bad prognoses are likely to be referred to him, so that in his practice there would be a higher proportion of complications. Any comparison would therefore be badly biased.

Gross biases are likely to occur if comparisons are made between two countries (different reporting methods), between two hospitals (different admission regulations), or even between services in the same hospital. Often biases can occur within a study if, for example, the reading of x-rays is divided between two physicians who use different standards.

To make matters worse, statistical tinkering is generally an unsatisfactory way to deal with bias. Fancy "adjustments" designed to avoid a suspected

bias may very well introduce an unsuspected bias. While it is hard to *remove* bias from data it is relatively easier to keep the biases from getting in in the first place. *The time when a statistician can help most is before a study starts, not after the results are in.*

A reader does not have to be an expert in order to recognize a well-designed medical study because the principles of good design are common-sense ones. If a study is poorly designed a reader will do well to be wary of the conclusions no matter how fancy the "statistics" may appear. Of course the reader should realize that there are various *types* of studies and sometimes it is impossible to put some of the principles in effect. Thus in a forward-going study the allocation of treatments is under the control of the experimenter whereas in a backward-going study of records the treatments have already been allocated. We can only ask for good design *within the limitations of the particular type of study.* These limitations will, nonetheless, affect our confidence in the results of the study.

A Design Check List.—

1. *Is the author aware of the possible biases in his study?* Does the author in his discussion (or in his actual design) indicate that he understands that unsupported diagnoses, haphazard allocation of treatments, and various other factors may introduce biases?

2. *Are the patients in the series selected in an objective fashion?* Did the author set down in advance the standards that would be used in deciding whether or not a patient would be counted in the series or do the authors seem to "play by ear" in rejecting some patients from the series?

3. *Is there a genuine control series?* Frequently a comparison series is chosen which is a control in name only. Either a control series must be obtained in essentially the same way as the series under study or it must be obtained by some matching process (or both). Arbitrarily chosen comparison series may be worthless as controls.

4. *Is the allocation of patients to treatment accomplished in an objective fashion?* Very serious biases may be introduced if this allocation depends on the personal choice of the experimenter or is haphazard. In a forward-going study the allocation should be made either by a systematic objective method (for example, alternating patients, alternating days, etc.), or by a random method (such as flipping a coin) at *some* stage.

a. It is not necessary that the allocation be completely at random, e.g., it may be desirable to set up specific therapies for specific classes of patients (for instance, sex, age, stage) in conformity with best medical practice. The allocation of *acceptable* treatments would then be made at random.

b. A random allocation is not the same thing as a haphazard allocation. A random allocation follows a carefully prescribed procedure which involves no individual choice.

5. *Do the authors make an effort to have uniformity in their study for the factors other than those under study?* Frequently authors are interested primarily in, let us say, the effects of a drug, but this drug may represent only part

of the therapeutic measures. If the other therapeutic procedures are quite variable, then evidently it is going to be very difficult to separate their effects from the drug effects.

6. *Do the authors try to balance or match their series so as to control factors known to be important?* For example, if stage or grade is known to be an important factor in the prognosis, does the author try to equalize his series in these respects? In general (though there are some exceptions) the most effective comparisons are made between two series of approximately equal length.

7. *Is the experiment blind or double blind?* In a blind experiment the patient does not know the particular therapy that is being given to him. For example, if a series of analgesic drugs are being tested, all of the drugs are compounded to appear identical in appearance and taste. In a double blind experiment the doctor, as well as the patient, does not know what has been given (although, of course, a third party is informed and will provide the information if absolutely necessary). Blind experiments are designed to avoid biases arising from psychological factors, factors which may exert a surprisingly large influence on the results.

Some Case Histories.—A reader who is acquainted with the principles of good design just mentioned and who appraises the actual design of a study in this light will be able to make a fair judgment of the reliability of an author's conclusions. Since no amount of statistical mumbo jumbo can undo the damage caused by poor design, an appreciation of design principles is really more important than an understanding of statistical technicalties.

Of course, it does not follow that poor design, ipso facto, leads to the wrong conclusions. Nevertheless, it is a good warning signal. Here are some examples of what can go wrong:

In the East South Central states there were 20,045 cases of malaria in 1946, according to the National Office of Vital Statistics. In 1947 there were 1,487 cases in this region (according to the same source). Was there a real eradication of malaria in this area? No, what happened was that the *definition* of malaria had been changed and by 1947 positive laboratory evidence was required before a case was counted, whereas previously diagnosis by symptoms was sufficient. Similar (but less spectacular) differences in basic definitions and procedures can produce serious bias in comparisons of two series and this is why a genuine control series is essential.

In a study of exchange transfusions for erythroblastosis fetalis it was found that mortality was very low for blood from female donors and very high for blood from male donors. Since this fact was not discovered until after the study was completed, it might seem very unlikely that the allocation of patients to treatment (i.e., blood from donor of a given sex) could have been biased. However, later investigation indicated that at the time the study was instituted it was generally believed that blood with higher hematocrits was superior and since male blood tended to have higher hematocrits this almost inevitably resulted in the selection of male blood for the more severe cases and, as a last step in this chain, a much higher mortality for male blood.

Later studies have indicated that the sex of the donor has little or no influence on the results. As long as allocation to treatment depends on individual judgment, subtle biases of this kind are likely to lead to erroneous conclusions.

Psychological biases may have startling effects. A new treatment gave excellent results for a while and then suddenly became no better than the other treatments. It was noticed that the turning point happened to coincide with a change in receptionists. It turned out that the first receptionist, who knew which patients received the new treatment, always congratulated these people on their appearance of well-being. This psychological shot in the arm showed up in the earlier results.

Where Do We Go From Here? Attention to the points listed in connection with sampling variation and bias will protect you from many of the pitfalls in the medical literature. If you want to understand the more technical details of a paper or if you are planning to use statistical methods in a paper of your own, you will, of course, want positive knowledge rather than negative protection. Books by Mainland[1] and Bradford Hill[2] contain excellent discussions of the rules for statistical evidence in medicine with formulas and computational examples. My book[3] gives a general discussion of the ideas of statistics without going into computational and methodological details.

References

1. Mainland, Donald: Elementary Medical Statistics, Philadelphia, 1952, W. B. Saunders Company.
2. Hill, Bradford: Principles of Medical Statistics, New York, 1952, Oxford University Press.
3. Bross, Irwin: Design for Decision, New York, 1953, The Macmillan Company.

Discussion

DR. THOMAS L. BALL.—Many of us have engaged upon a study, or more properly a systematic compilation, in which we record statistics. We arrive at a great many conclusions but the statistical material actually belongs in the Annual Report of the Hospital. I think we have to distinguish between a study in which an original observation is made and a study in which a group of patients are simply compared, without the aid of a professional statistician.

Dr. Corscaden makes a very important point in discussion of the incidence of carcinoma of the cervix and of the fundus. As taught in most textbooks, the woman between 45 and 55 years of age has the highest peak incidence of carcinoma of the cervix. Between 55 and 65 years of age there exists the highest peak incidence of carcinoma of the fundus. As the average textbook reads, one would suspect that if you were between the ages of 45 and 55 years of age you should have more chance of getting carcinoma of the cervix than you do later on in life. What must be remembered is that more women in this age group are alive and seeking gynecological care. Other diseases having taken their toll, fewer are alive at the age of 70 to develop cancer. The longer you live, the higher is your chance of developing cancer. With carcinoma of the fundus the situation is similar. The longer a woman lives, the more chance she has of getting cancer of the fundus in any one year. Therefore, to teach students that the peak incidence of cancer of the cervix is between 45 and 55 is untrue. One should say, "Most patients one sees with cancer of the cervix are between 45 and 55 years of age."

DR. ROY W. BONSNES (By invitation).—We should remember that statistics is a branch of probability mathematics. As such, it is a part of logic and it is absolute and

correct. Bertrand Russell has said that the problem arises when you try to apply probability mathematics to reality. That is a problem that we are all faced with when we use this branch of mathematics and apply it to patients.

There is a great deal to be learned from statistics, however, a great deal that can be of use and can be applied to the problems that are faced in the practice of obstetrics and gynecology. A statistician can be of help in the application of the data which have been arrived at by objective statistical procedures to the particular patient whom you may have to treat.

DR. BROSS (Closing).—I would like to comment on one of the remarks that has been made about the subject of statistics, because I cannot agree with it. Statistics is not, in so far as I am concerned, an abstract mathematical discipline. It is a way of applying experience in a systematic fashion. I think that the information you get from statistics applies to the individual patient because it is a summary of the experience you had in past patients. It tells you, as it were, what is your best bet—what line of action is most promising and most likely to lead to success. More than this I do not believe you can ask for.

PREGNANCY AND PELVIC TUBERCULOSIS

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MUCH has been written concerning the woman with pulmonary tuberculosis who becomes pregnant. Relatively few observations have been made on the occurrence of pregnancy in the presence of secondary pelvic tuberculosis, possibly because of the rarity of this association. While there is a growing recognition at the present time of the importance of this disease as a factor in sterility, pregnancy has been regarded as impossible[1] or very uncommon[2, 3] in the presence of pelvic tuberculosis.

It is generally agreed by all students of tuberculosis that the involvement of the pelvic organs in this disease is secondary to a primary focus, usually situated in the lungs. There are probably few exceptions to this sequence of events.[4, 5] The present concept of the dissemination of pulmonary tuberculosis holds that the hematogenous spread of the disease and the subsequent development of secondary foci take place as a rule during the active development of the initial pulmonary lesion, known as the primary complex. *This concept is important to hold in mind since it predicates the initiation of secondary foci in most patients within one year of occurrence of the primary complex and not as a late manifestation. Such secondary lesions may give rise to immediate clinical manifestations. Frequently they remain latent for long periods of time to terminate by healing or by giving rise to a subsequent tuberculous process.* This concept readily explains the common experience that a primary pulmonic lesion cannot be demonstrated by x-ray or clinical studies in many patients with proved tuberculous salpingitis. On the other hand, historical evidence can frequently be obtained of antecedent pulmonary disease or other primary tuberculous infections in such patients. Winkler and Wegemer[6] obtained a history of a preceding attack of pleurisy, generally within five years, in 41 per cent of their cases of pelvic tuberculosis, whereas only 3 of their 95 cases showed positive pulmonary findings on x-ray of the chest. In 125 cases of genital tuberculosis, Jedberg[5] obtained a previous history of one or more earlier tuberculous lesions outside the pelvis in 67 per cent. It is evident from both clinical and pathological studies that the primary complex in the lung frequently heals, leaving secondary foci in the pelvic organs which may give rise to clinical evidence of disease several years later.

This paper is not concerned with the patient suffering from advanced pelvic tuberculosis. Here the marked pathological changes have led to destruction of tubal function so complete that one can readily grant that preg-

nancy is impossible.[7-10] It is concerned with the considerable number of women, recorded during the past thirty years, who have been discovered to have what has been termed latent or subclinical pelvic tuberculosis.[2, 11-14] These women uniformly have the presenting complaint of sterility, often primary with or without associated symptoms such as alteration of the menses, vaginal discharge, etc. Pelvic examination usually results in normal physical findings. The discovery of tuberculosis of the pelvic organs is made ordinarily on the examination of curettings or an endometrial biopsy and comes as a complete surprise to the physician. Absolute confirmation of the nature of the endometrial infection can be made by culture of menstrual blood or endometrium; in addition, the latter tissue can be implanted into animals.[5, 10, 15-17] Such studies have resulted in the recovery of tubercle bacilli in a varying proportion of patients in whom the endometrium appears histologically tuberculous. The organism in over 90 per cent of instances has been of the human type.[5, 10] The presence of tuberculous endometritis predicates almost certainly an associated bilateral tubal infection, although the physical alteration of the oviduct cannot be detected on examination; in such cases definite stigmas may be present at laparotomy. As will be shown, however, the tubal lesion may escape detection even under inspection and palpation at the time of operation (Cases 4 and 5). This has also been noted at autopsy.[18] This assumption must be made in view of the well-known distribution of this disease in the pelvic organs, i.e., solitary endometrial tuberculosis is very rare; almost 100 per cent of cases of endometrial tuberculosis will show an accompanying tuberculous salpingitis. The former lesion is found only in 60 to 70 per cent of patients with tubal involvement.[7-10]

The first discovery of the subclinical type of pelvic tuberculosis in any large number of women must be credited to Steinsick,[11] who first employed routine curettage in the investigation of sterile women. In 1922, among 212 patients, he discovered 7.2 per cent with tuberculous endometritis. Subsequent observers report an incidence ranging as high as 5 and 10 per cent in sterile women.[2, 12-14] These are all reported from areas outside the continental United States. The greater prevalence of pelvic tuberculosis in these areas has been laid to environmental factors, but it is to be suspected that careful search will reveal a considerable number in our own population. This is borne out by the report of Rock and Bartlett,[19] who stated that it was discovered in 8 of 437 sterile women (1.8 per cent). In 7 of them it was quite unsuspected. Further investigation of such patients has demonstrated the fact that tubal patency may still be present in one-fourth to one-third.[2, 12-14] Prolonged follow-up has shown that many remain in this subclinical phase for extended periods of time.[2, 12] In some cases the disease heals, while in a minority progression to clinically recognizable pelvic tuberculosis occurs and eventually demands surgical therapy.[2, 12] Some of the latter group develop general dissemination of the disease so that this type of lesion cannot be regarded as entirely without risk to the patient.[3] It can be estimated that cases of subclinical pelvic tuberculosis far exceed the group showing definite pelvic findings and symptomatology.

The following 3 cases are illustrative of the latent or subclinical variety of pelvic tuberculosis:

CASE 1.*—(Sloane Hospital No. 258,259) Mrs. I. S., aged 33 years, white, married seven years, para 0, gravida 0, was subjected to study in 1935 because of sterility. Her only previous illness had occurred at the age of 21 when she was suspected of having tuberculosis of the cervical spine and had suffered from a dry pleurisy for several months. Careful follow-up had revealed no evidence of a pulmonary lesion and recent chest x-rays showed negative findings.

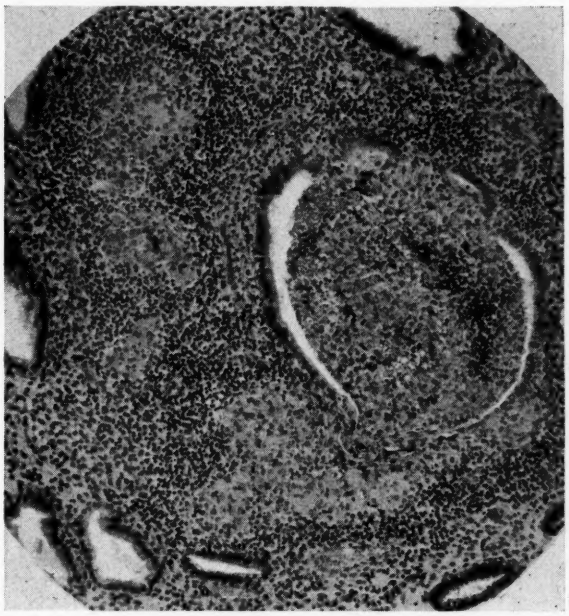

Fig. 1.—Tuberculous endometritis discovered in curettings from Case 1.

Her menstrual history was normal. Bimanual and speculum examination revealed nothing abnormal. Her husband was not a factor. Transuterine insufflation showed patent tubes. A basal metabolism rate of minus 11 was discovered and she was put on thyroid. Since no pregnancy occurred as a result of this investigation, she consulted another doctor in 1937, who reviewed the previous procedures and, noticing the omission of a curettage, carried out this procedure on Dec. 14, 1938. The curettings showed abundant tubercles (Fig. 1), a finding that was confirmed at a second curettage performed several months later. This patient was followed over the next ten years. She never became pregnant and palpable abnormalities could never be found in the pelvic organs. She stopped menstruating at the age of 42. She was last seen in 1947, at which time no evidence of progression of the disease could be found on pelvic examination. An attempt has been made to find this patient but contact could not be made.

CASE 2.—(Bellevue Hospital No. 34732-43) Mrs. S. F., aged 26 years, white, para 0, gravida 0, was admitted to the gynecological service of Bellevue Hospital on July 23, 1943, because of a uterine hemorrhage following an attempt at transuterine insufflation by her private physician. She had been subjected to this procedure every two weeks for the past four months following the discovery that the tubes were not patent and on one occasion had been told that positive results had been attained. She gave no history of any illness. Her menstrual history was normal. General physical examination proved negative. Pelvic examination revealed normal findings except for a bloody vaginal discharge.

*Reported through the courtesy of Dr. D. A. D'Esopo.

Examination under anesthesia revealed no abnormal findings. A curettage secured endometrial fragments which, on microscopic examination, revealed a secretory pattern and which contained many typical tubercles (Fig. 2).

An attempt was made to get this patient back for follow-up examination in 1948. She stated that she was quite well, was under the care of a private physician, and was about to undergo an operation to re-establish tubal patency. It was suggested to her that it would be wise for her doctor to get in touch with the Bellevue Service. Nothing further was heard, either from her or from her physician.

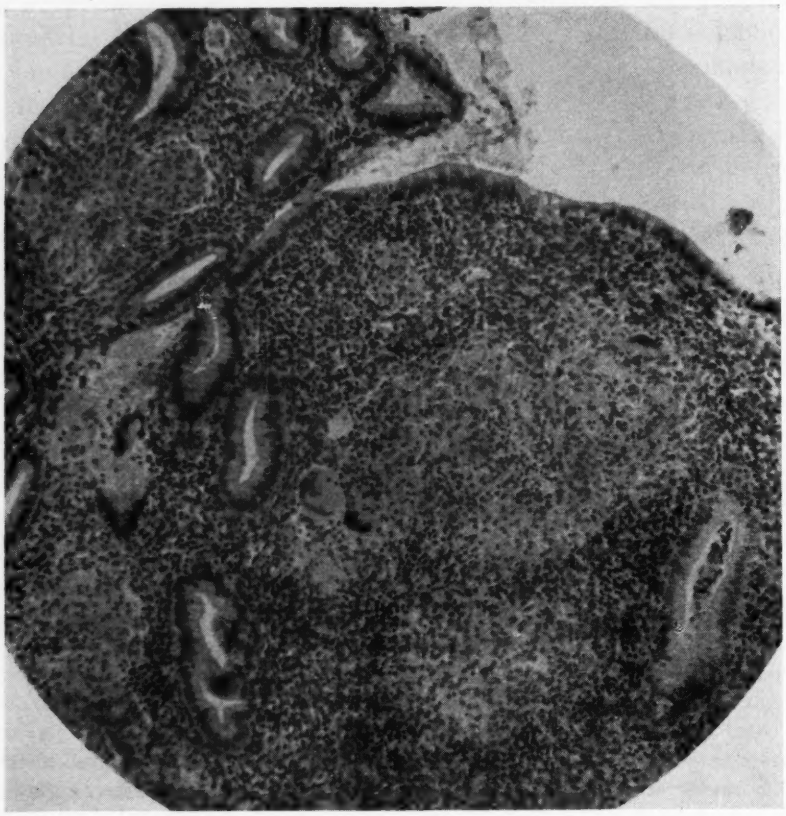

Fig. 2.—Tuberculous endometritis discovered in curettings from Case 2.

CASE 3.—(Doctors Hospital No. 53-955) Mrs. G. M., aged 40 years, white, para 0, gravida 0, was admitted to the Doctors Hospital on Feb. 1, 1953, for the removal of a left ovarian tumor about 10 cm. in diameter. She had been married 15 years and had never been pregnant. Transuterine insufflation and hysterograms early in this period had revealed occluded tubes. She was told that otherwise the pelvic organs were normal. She gave no antecedent history of tuberculosis or of abdominal symptoms. Her menses were normal until the age of 38 when they abruptly ceased. She had been on estrogen therapy and recently had two periods accompanied by severe crampy pain.

General physical examination was negative. Bimanual examination revealed a movable 10 cm. mass in the region of the left ovary. Otherwise the pelvic organs seemed normal.

At laparotomy an obvious dermoid cyst of the left ovary was discovered. Both tubes were densely adherent to the posterior aspect of the broad ligaments and showed occlusion of the fimbriated extremities. A total hysterectomy and bilateral salpingo-oophorectomy were performed. Pathological examination showed a bilateral healed salpingitis. The right tube

showed areas of calcification. The left tube, after further sections were cut, showed a small area containing typical tubercles. The endometrium was normal and failed to show these lesions (Figs. 3 and 4).

Fig. 3.

Fig. 4.

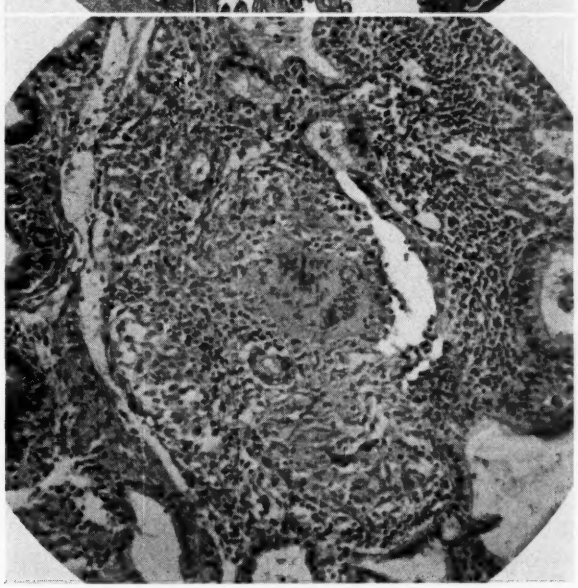

Fig. 3.—Chronic healed salpingitis with calcification in right tube of Case 3.

Fig. 4.—Tubercles discovered in chronic healed salpingitis of left tube after search in many sections (Case 3).

These three examples of subclinical pelvic tuberculosis illustrate various characteristics of this disease. The absence of symptoms and abnormal pelvic findings and the uniformity of the presenting complaint of sterility are noteworthy. All of them emphasize the fact that such cases do not always progress

but remain static over long periods of time.[2, 20] In fact, some observers feel that this is the rule rather than the exception. Case 3 points to the possibility of such a lesion healing spontaneously. Case 1 represents the variety with which this paper is concerned. In this patient tubal patency was repeatedly demonstrated, and here the possibility of pregnancy exists yet it rarely occurs. Sharman[2] states that he has followed 127 such individuals from one to fifteen years and pregnancy occurred in only one case. Others have had a similar experience.[5, 12] What is the factor which prevents the occurrence of pregnancy? It is most difficult to believe that the endometrial lesions, often few in number, and readily missed in single microscopic sections, would prevent

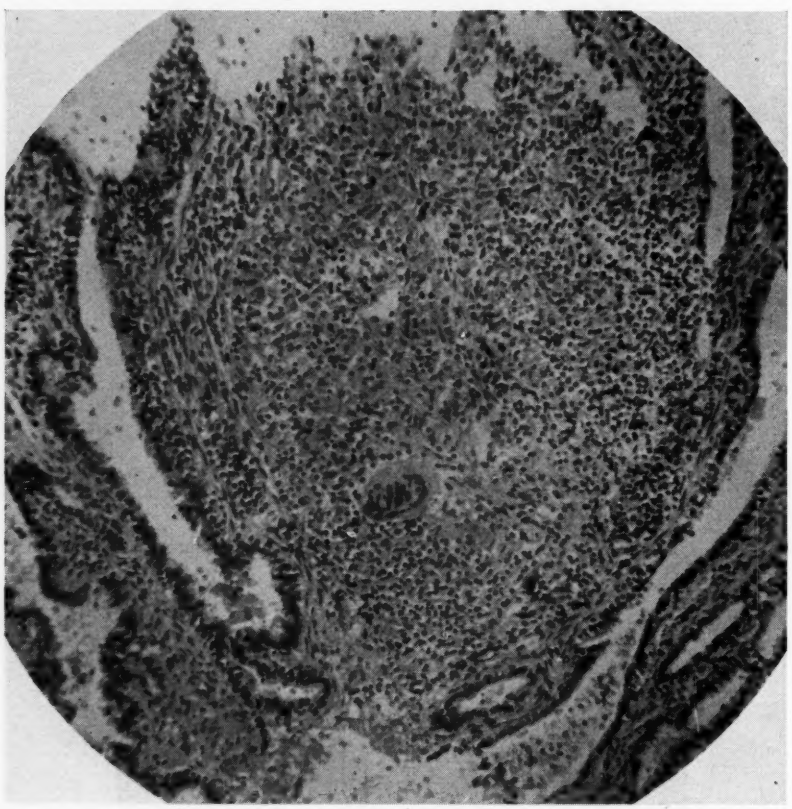

Fig. 5.—Tuberculous salpingitis discovered in section of left tube made at point remote from site of tubal gestation (Case 4).

nidation. The failure of pregnancy to take place can be ascribed in all probability to the profound alteration of the tubal mucosa, producing a very extensive follicular salpingitis, which has on occasion been misinterpreted as a tubal carcinoma until multiple sections revealed the true character of the lesion.[8] It may well produce a labyrinthine maze which traps and delays the sperm in its ascent, allowing degenerative changes to begin before it comes in contact with the ovum. In addition, the tubal infection may produce an en-

Fig. 6.—Very low power of left tube at point remote from site of ectopic gestation, showing marked fusion of secondary plica to form follicular salpingitis but main pathway through tube patent and free from exudate (Case 5). (×15; reduced ¼.)

Fig. 7.—Higher magnification showing glandular pattern of follicular salpingitis characteristic of tubal tuberculosis. Tubercles may be absent in large areas (Case 5). (×90; reduced ¼.)

Fig. 8.—Tubercles in mucosa in another area (Case 5). (×200; reduced ¼.)

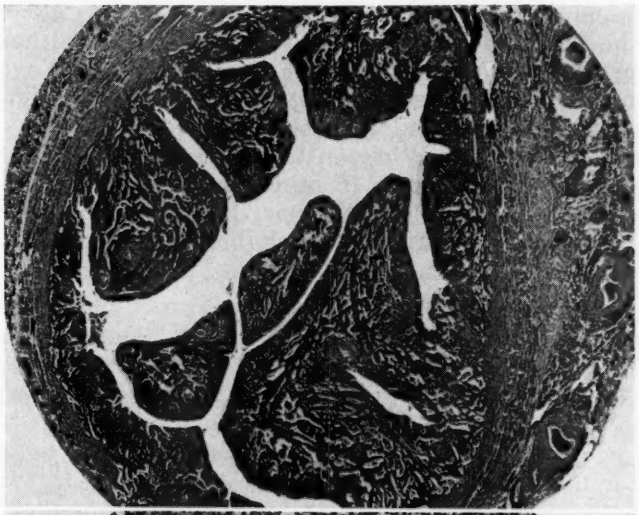

Fig. 6.

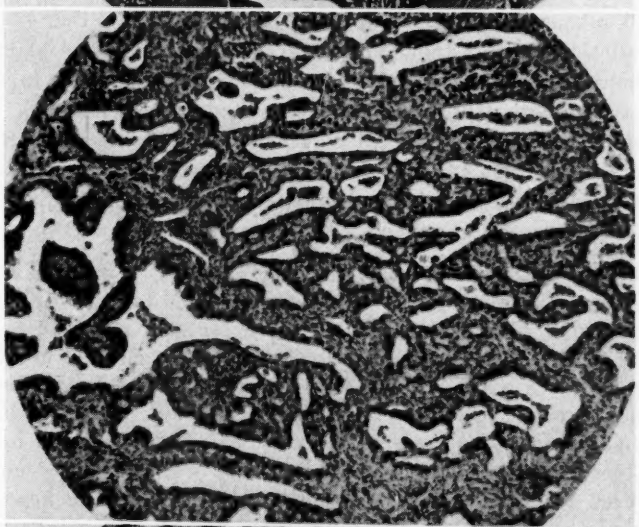

Fig. 7.

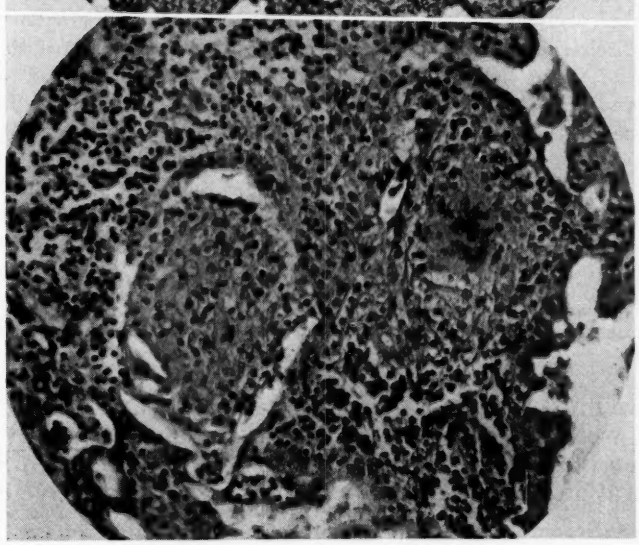

Fig. 8.

(For legends see opposite page.)

vironment inimical to both sperm and ovum. The possibility of this factor is favored by the fact that even ectopic pregnancy is rare, although large numbers of these patients are capable of becoming pregnant. Nevertheless, pregnancy can occur, as is witnessed by the growing numbers of ectopic gestations reported as occurring in tuberculous tubes.

In 1939, Stevenson and Wharton[21] reported the first such case in the American literature and collected 16 others from foreign sources, 7 of them of the abdominal type. By 1951, Kistner, Hertig, and Rock[22] were able to assemble 52 of these cases. Nothing remarkable was noted in the postoperative course of such patients. To these can be added 3 others, 2 of them occurring sequentially in the same patient.

CASE 4.*—(Sloane Hospital No. 706680) Mrs. V. H., aged 32 years, white, married, para 0, gravida i, had her last normal period on Feb. 13, 1943, and sought medical care on April 21, 1943, because of bleeding and lower abdominal pain of eleven days' duration.

Her previous menstrual history was normal. She had been suspected of having pulmonary tuberculosis in 1937 but had been told in follow-up that the lesion was healed.

General physical examination was negative except for tenderness, muscle resistance to palpation, and rebound tenderness in the lower abdomen. Pelvic examination showed findings characteristic of a left tubal pregnancy. This was verified at laparotomy, a left tubal abortion being excised. The pelvic peritoneum and the right tube showed no evidence of pelvic tuberculosis, the latter being reported as quite normal. Pathological examination of the left tube showed typical chorionic villi and a tuberculous salpingitis (Fig. 5). A chest x-ray was taken before discharge and proved normal. She was last seen in 1944. No further pregnancies had taken place and pelvic examination revealed no abnormal findings.

CASE 5.—(Sloane Hospital No. 6704) Mrs. M. O., aged 33 years, para 0, gravida i, had her last normal period on July 29, 1924. She was admitted to the hospital on Jan. 8, 1925, complaining of irregular bleeding, cramps in the lower abdomen, and backache for three months. Her menstrual history was normal. Her previous medical and surgical histories were irrelevant and there could be elicited no suggestion of tuberculous infection. General examination was negative except for the presence of a tender mass in the left lower quadrant of the abdomen rising from the pelvis. This was confirmed on pelvic examination. At laparotomy a ruptured left tubal pregnancy was discovered and removed. The right tube appeared slightly swollen and congested but otherwise normal. Pathological examination of the specimen showed an ectopic pregnancy in a tuberculous tube.

Following discharge she was seen several times and then referred to the Presbyterian Hospital because of vague lower abdominal complaints which suggested tuberculous peritonitis. She received heliotherapy and small therapeutic doses of x-ray. The latter was discontinued because of the possible sterilizing effects. Her menses continued in a normal pattern and repeated pelvic examination showed no abnormal findings.

She again experienced amenorrhea dating from June 6, 1926, followed by the onset of severe lower abdominal pain for which she was readmitted to the hospital. Examination revealed clear-cut evidence of a right tubal pregnancy, and she was subjected to laparotomy. A ruptured right tubal pregnancy was removed, which on pathological examination revealed, in addition, tuberculous salpingitis. She was seen for the last time in September, 1926, at which time she had no complaints and revealed nothing abnormal on examination (Figs. 6, 7, and 8).

These cases illustrate the minimal alteration of the external characteristics of the oviduct which is present in some cases of subclinical pelvic tuberculosis. One can assume that both tubes were involved in these patients at the time of the initial operation and in one of them there is fairly positive evidence to this

*Permission to report this case was given by Dr. Marion D. Laird.

effect. Yet, if the lesion was not detected by direct vision and palpation, how can it possibly be discovered on bimanual examination? In view of the profound alteration of the tubal mucosa occurring in minimal tuberculous salpingitis, it is not difficult to imagine sufficient interference with tubal function to delay the transportation of the fertilized ovum, thus favoring an ectopic rather than a uterine nidation. The puzzle appears to be that the combined process is not encountered more often.

Finally, one comes to the question of whether uterine pregnancy can occur in the presence of this complication. Certainly, if it is possible for ectopic pregnancy to take place in such a patient, under very fortuitous circumstances intrauterine pregnancy can occur. The fact that it has seldom been observed in a known case of subclinical pelvic tuberculosis simply emphasizes its rarity. That intrauterine pregnancy has a relationship to pelvic tuberculosis has been observed repeatedly. Greenhill,[23] in 1921, reviewing 200 cases of tuberculous salpingitis, noted that pregnancy in some form was associated with the acute onset of detectable pelvic inflammation in about 13 per cent. This relationship has been noted recently by others.[17, 24] In 1924, Feuillade[25] reviewed the European literature in regard to this subject and was able to divide his material into two groups: (a) Seven women became pregnant five to ten years after conservative medical or surgical therapy for tuberculous salpingitis. In these the disease presumably had healed. One of them aborted; 6 carried pregnancies to term; only one had any puerperal complication. (b) Seventeen women became pregnant within a short period after the discovery of pelvic tuberculosis. The fact that the lesion was still active was demonstrated by the disastrous effects both to the mother and to the gestation. Only 5 of these pregnancies went to term. Three of the 5 infants died of tuberculosis within a few months so that only 2 living infants resulted in the entire group. The maternal loss was equally serious since 16 of the 17 mothers had severe exacerbations of tuberculosis, usually in the pelvic organs. Only 6 recovered and 4 of these underwent radical pelvic operations. He concluded that uterine pregnancy taking place in the presence of active pelvic tuberculosis resulted disastrously, but that there was little danger if the lesion had healed. Stevenson and Wharton,[26] in 1939, noted the latter article but stated that they could find no reference to this condition in the American literature. Fruhinsholtz and associates[27] in 1941 were able to collect 60 cases, mainly from the European literature. They noted the frequency with which abortion took place in such patients followed by a violent exacerbation of the pelvic infection and sometimes by widespread dissemination. Finally, Bobrow, Blinick, and Soichet[28] in 1953 have reviewed the recent literature and have reported a case in which it can be presumed that pregnancy took place in the presence of pelvic tuberculosis. This woman aborted at the third month. This event was followed by a violent pelvic infection which was found to be tuberculous in nature.

Since 1935, 5 patients have been observed at Bellevue Hospital who exhibited a similar sequence of events. One of these cases will be reported in some detail since the patient has been under observation from the onset of her tuberculosis so that the complete background of the disease is known. The others will be reported as briefly as possible.

CASE 6.—(Bellevue Hospital No. 18596-47) Mrs. C. R., aged 24 years, white, para 0, gravida i, was transferred on June 16, 1947, to the gynecological service from the chest service at Bellevue Hospital because of bleeding and cramps followed by a spontaneous complete abortion at about the third month of her first pregnancy.

Her menstrual history was normal. The last period was on March 9, 1947. Her previous medical history was of considerable interest. There was no history of tuberculosis in her immediate family. She entered the Bellevue Training School for Nurses at 16,

and up to September, 1943, just before graduation, showed a negative Mantoux test. At this time the test became positive just after she completed two weeks' assignment to the chest service. Following this finding, monthly chest x-rays were taken and in December, 1943, a pleural effusion was noted on the left. One week before she had slight pleural pain in the same area. Her temperature was 99.6° F. A week later the pain was gone. She was admitted to the chest service from January to March, 1944. The fluid disappeared without thoracentesis. Aspirated gastric contents were found negative for tubercle bacilli on three occasions. X-rays of the chest failed to reveal any parenchymal lesion. She was then transferred to Stoneywald Sanatorium where she received three more months of complete bed rest, followed by six months of limited activity, and finally five months of graduated activity. The sputum, cultures, and x-rays during this time were all negative. In May, 1945, she returned home and returned to Stoneywald from November, 1945, to February, 1946. She returned to Bellevue Hospital as an instructress in nursing at this time and continued to be carefully followed. She was married in September, 1946. A premarital examination revealed no abnormal pelvic findings. Near the end of April, 1947, she had a slight hemoptysis. This had been preceded by right pleuritic pain of one day's duration occurring about one week before. She was immediately admitted to the chest service at Bellevue Hospital where an x-ray showed for the first time a small parenchymal lesion at the right apex. The sputum was negative. She believed herself to be pregnant and an Aschheim-Zondek test proved positive. Pelvic examination on two occasions revealed an apparently normal intrauterine pregnancy with no suggestion of any adnexal lesion. Therapeutic abortion was considered, but was rejected by the patient.

Course on the gynecological service: Immediately after the occurrence of the abortion, her temperature rose to 102° F., and during the next four weeks it was remittent in character, ranging from 103 to 104° F. At the end of forty-eight hours, examination showed the abdomen to be moderately distended and tenderness was present on pressure above the pelvic brim. On bimanual examination the cervix was found to be closed, the uterus anterior, firm, small, and the left adnexa to be thickened, palpable, and tender. During the next week she developed bilateral adnexal masses, the largest on the right, accompanied by extensive parametritis. She complained of abdominal pain, sleeplessness, and suffered bouts of vomiting lasting two to three days. Repeated blood cultures were given. Chest x-rays showed no change in the pulmonary findings. The red blood cell count showed a moderate anemia. Repeated white blood cell counts were normal with a tendency to leukopenia. She was treated with sulfonamides, penicillin, and repeated transfusions with little effect. On July 15, 1947, streptomycin was started, 2 Gm. daily being given in four doses. Within forty-eight hours the temperature dropped to normal and marked subjective improvement took place. She received a total of 20 Gm. over a ten-day period, with no evidence of toxicity. The fever did not recur after discontinuance of the drug.

On July 28, 1947, she was transferred back to the chest service. At this time an 8 cm. mass was noted in the right adnexa and the left tube was elongated, thickened, and fixed. She remained there until Nov. 14, 1947. During this time the rectal temperature was 99 to 99.4° F., no further changes were noted in the chest x-rays, and the sedimentation rate fell from 57 to 20 mm. (Westergren). No change was noted in the pelvic findings, except for the disappearance of tenderness. She complained of frequent and prolonged menstruation.

On November 14 an exploration of the abdomen was carried out. A marked fibroadhesive tuberculous peritonitis was found. The uterus and adnexa were bound in adhesions and were not visualized. Bilateral adnexal masses were palpated. A biopsy of the omentum was taken and the abdomen was closed. Streptomycin was instituted, a total of 18 Gm. being given, 2 Gm. a day for four days and 1 Gm. a day for 10 days. She was febrile for three days and on the tenth day an infected hematoma was drained. The wound healed quite soundly following this. On December 1, an endometrial biopsy was taken. Pathological examination of the omentum showed tuberculosis. Examination of the endometrial biopsy showed tuberculous endometritis. She was returned to the chest service on Dec. 3, 1947, from which she was sent to Stoneywald Sanatorium on March 4, 1948. Exam-

ination just prior to this showed an 8 cm. mass in the right adnexa and a smaller mass on the left. Slight mobility was present. During the next nine months her chest lesion diminished and stabilized. Pelvic examination in December, 1948, after her return to New York City, showed slight thickening in the right adnexa and a 4 by 5 cm. mass on the left. Cultures from the cervix were negative for acid-fast organisms. Repeated examinations showed further improvement. At present slight thickening can be felt in the right adnexa. For the past year she has returned to active work at Bellevue Hospital. She is quite symptomless except that she has not become pregnant.

CASE 7.—(Bellevue Hospital No. 7943-35) Mrs. J. C., Negro, aged 24 years, married, para 0, gravida i, was admitted in the third month of pregnancy on March 27, 1935, complaining of pain the lower abdomen and vaginal bleeding for four days.

She had been admitted to Seaview Hospital in May, 1934, for pulmonary tuberculosis, where she was kept for six months and treated by right pneumothorax. She had been discharged in January, 1935, as an arrested case but had continued the same treatment up to the present. An appendectomy had been performed in 1929.

General physical examination on admission was negative except for a temperature of 99.4° F. and physical signs of pneumothorax on the right side of the chest. Bimanual examination showed the uterus enlarged to the size of a three months' pregnancy. Nothing abnormal was noted in the adnexa. On inspection the cervix was blue, showed a scant bloody discharge. A diagnosis of threatened abortion complicated by chronic pulmonary tuberculosis was made.

About twenty-four hours later she aborted completely, the fetus appearing to be about 14 weeks of age. Unfortunately, the placenta and membranes were not subjected to pathological examination.

Immediately following the abortion her temperature rose to 101° F. and within the next few days to 104° with a corresponding elevation of pulse rate. Examination on April 3, five days after the abortion, showed a uterus enlarged to twice normal size with marked adnexal tenderness but no definite masses. She was believed to be suffering from postabortal sepsis, secondary to unadmitted interference or to gonorrheal cervicitis. Cultures showed a mixed flora of organisms; no hemolytic streptococci or gonococci could be recovered in special media.

This course persisted for four weeks, the temperature ranging between 101 and 104° F. Later pelvic examinations showed the uterus to be retroverted with a tender mass behind it in the cul-de-sac.

Early in May the temperature began to fall to lower levels but she began to develop evidence of intestinal obstruction. On May 10 an exploration was carried out. A large amount of fecal fluid and gas was encountered in the peritoneal cavity. The peritoneum was studded with tubercles and many adhesions were present. The perforation could not be located. She died two days later. An omental biopsy was reported as showing tuberculosis.

At autopsy the principal findings were: (1) caseous pulmonary tuberculosis in the right middle lobe, the right lower lobe, and the left lower lobe with hematogenous spread to the left lung; (2) tuberculous peritonitis; (3) tuberculous salpingitis (bilateral, the tubes not occluded); (4) tuberculous metritis and endometritis; (5) tuberculous cervicitis; and (6) perforation of the appendix stump.

CASE 8.—(Bellevue Hospital No. 27614-44) Mrs. A. K., aged 23 years, white, para 0, gravida i, was admitted on June 15, 1944, complaining of purulent vaginal discharge, pain in the lower abdomen, and fever, dating from spontaneous abortion which had occurred at about the twelfth week of pregnancy, eight weeks prior to admission. Her previous medical and surgical histories were irrelevant. Her menstrual history was normal. She had married in January and became pregnant almost immediately.

General physical examination revealed nothing except for a tender mass over the lower abdomen. Bimanual examination revealed a tender, fixed right adnexal mass. A diagnosis of postabortal salpingitis was made.

Her temperature was 101.4° F. on admission and followed a remittent course with daily rises to 103° with occasional chills. She was given penicillin for 10 days with no effect.

After six weeks of palliation she was subjected to a laparotomy on Aug. 18, 1944. A general adhesive tuberculous peritonitis was discovered. The uterus and adnexa could not be discovered but the thickened, fixed right adnexa could be palpated through the adhesions. After an omental biopsy was taken, the abdomen was closed. Her postoperative course was uneventful and she was discharged on Sept. 1, 1944. A chest x-ray taken in the postoperative period showed no evidence of a pulmonary lesion. The pathological report on the omental biopsy showed tuberculosis.

After leaving the hospital, she went to Florida for a year. On her return she had no complaints except that she had not become pregnant. A residual mass measuring 8 cm. in diameter could be felt in the right adnexa. Examination in 1952 showed no palpable adnexal mass.

CASE 9.—(Bellevue Hospital 42785-46) Mrs. J. P., aged nineteen years, married, white, para 0, gravida i, was admitted on Sept. 19, 1946, complaining of fever, generalized abdominal pain, diarrhea, and irregular uterine bleeding dating from the occurrence of a spontaneous abortion at the third month of pregnancy which had occurred twelve weeks previously. Shortly after the abortion she was curetted at another hospital. Her previous medical and surgical histories were negative. Her menstrual history was normal.

General physical examination revealed a poorly nourished, poorly developed, young white woman. A soft nontender mass rising to 5 cm. of the umbilicus was present in the lower abdomen. On bimanual examination the corpus could not be distinguished from the abdominal mass which was fixed and appeared to rise in the right adnexa. The left adnexa were thickened and fixed. A diagnosis of postabortal salpingitis was made. The temperature was 101° F. on admission and was remittent in type between 99 and 101° over the next five weeks. Penicillin had no effect and the findings remained unchanged.

On Oct. 14, 1946, she was subjected to laparotomy. An extensive tuberculous peritonitis was encountered which prevented actual inspection of the pelvic organs. A large abscess containing 200 c.c. of pus was opened in the region of the right adnexa. An omental biopsy was secured and this was reported as showing tuberculosis.

Her postoperative course was stormy and prolonged, marked by fever, partial breakdown of the operative incision, and sinus formation. Postoperative x-ray studies revealed no pulmonary lesion. In May, 1947, she began to show evidence of meningitis. At this time she was put on streptomycin. She showed temporary improvement but then relapsed and died on Sept. 27, 1947. No autopsy was performed.

CASE 10.—(Bellevue Hospital No. 47314-49). Mrs. J. M., aged 32 years, para 0, gravida i, was transferred from the chest service to the gynecological service at Bellevue Hospital on Nov. 16, 1948, with a diagnosis of tuberculous salpingitis.

She had been well until the summer of 1946 when she aborted her first pregnancy at the sixteenth week after ten years of marriage. Immediately after the abortion she began to suffer from lower abdominal pain and fever. A diagnosis of tuberculous salpingitis and peritonitis was finally made and this was confirmed at laparotomy. Biopsy specimens were secured and no further surgery was carried out. The abdominal wound never healed completely, a sinus remaining with persistent drainage. In October, 1946, she developed a chronic cough. She was admitted to Bellevue Hospital for the first time in April, 1947, and was found to have bilateral chronic hematogenous tuberculosis, a chronic abdominal sinus, and evidence of tuberculous salpingitis. She was treated with streptomycin and showed marked improvement, cultures of sputum, gastric contents, and cervical secretions becoming negative, the chest lesions diminishing, and the sinus healing. In March, 1948, a mass in the right breast was excised and found to be a tuberculous abscess. In July, 1948, it was thought that the adnexal masses had increased in size and she began to complain of lower abdominal pain. The sinus had reopened. A hysterectomy and bilateral salpingo-oophorectomy were recommended.

This was carried out without great difficulty on Nov. 19, 1948, after streptomycin therapy was begun three days before. It was continued for six weeks postoperatively. Her postoperative course was uneventful. She was sent back to the chest service on Dec. 10, 1948, and discharged on Jan. 29, 1949.

In 1950 she was readmitted for treatment of a psoas abscess. She is still under observation in the follow-up of the chest service.

These 5 patients presented a very similar clinical picture. All of them were young, all of them pregnant for the first time, in all of them the early weeks of pregnancy were quite uneventful. Spontaneous abortion took place in all 5 between the twelfth and sixteenth weeks of pregnancy, to be followed immediately by the onset of a severe pelvic infection characterized by lower abdominal pain, fever, and the development of adnexal masses. In the 4 observed during this part of their course at Bellevue Hospital the fever was of a remittent type, was prolonged over many weeks, and was not influenced by antibiotics except in one case in which streptomycin was used. This drug was not administered to the remainder prior to laparotomy. The latter patients showed either a leukopenia or a very slight leukocytosis. The sedimentation rate was rapid. In all 5 cases the presumptive diagnosis was postabortal sepsis, the true etiology being discovered only after a long delay in the performance of a laparotomy. Unfortunately, none of the aborted material was subjected to pathological examination. There is good reason to believe that the decidual and placental tissues would have shown tuberculous involvement. One patient (No. 9) was curetted following her abortion at another hospital. These curettings showed necrotic decidua containing round foci. However, all cellular detail was lost, so that those areas could not be identified as tubercles.

An earlier diagnosis might have been made if proper stress had been laid on the development of a severe pelvic infection characterized by a prolonged remittent fever following a spontaneous abortion. This is a most unusual sequence of events, in the absence of any interference, and, particularly in patients with a history of tuberculosis, should lead us in the future to suspect a tuberculous pelvic infection. Endometrial biopsy, direct cervical smears stained for acid-fast organisms, and cultures could be used to verify the clinical impression.

The question raised by these cases is whether the pelvic tuberculous infection was acquired during the early months of pregnancy or whether these patients became pregnant in the presence of a latent tubal infection. Direct evidence cannot be presented in any of them that the latter thesis was true. In only 2 (Cases 6 and 7) was a pelvic examination carried out prior to abortion. Neither of these patients showed any evidence of anything abnormal. This, however, does not rule out latent pelvic tuberculosis.

For presumptive evidence that the pelvic tuberculosis was antecedent to the pregnancy one must examine the general course of the disease in each patient. In Case 6 the entire course is known, the primary complex in the lung occurring four years prior to pregnancy. In Case 7 the primary complex probably occurred well over a year before pregnancy. Cases 8 and 9 showed no clinical or x-ray evidence of a pulmonary lesion and it seems probable that the primary complex had apparently healed without signs or symptoms at an undetermined time prior to pregnancy. No information in this regard is available in Case 10 which represents multiple widespread dissemination from a primary pulmonary lesion which failed to stabilize. Thus, in 4 of the 5 cases, it seems probable that the primary pulmonary lesion preceded the pregnancy by more than a year. This relationship would favor the presence of latent pelvic tuberculosis at the time that pregnancy took place.[4, 5]

As for direct evidence of the possibility of such a complicating uterine pregnancy, Jedberg has reported a case in which tuberculous endometritis was diagnosed by curettage shortly before the occurrence of pregnancy. This patient aborted at the third month and pursued a stormy postabortal course with the development of clinically obvious tuberculous salpingitis, the presence of which was proved at laparotomy. It is therefore our belief that this group of 5 cases all represent instances in which pregnancy has occurred in the presence of latent tubal infection and associated tuberculous endometritis.

Granted that this supposition is correct, it is an easy matter to reconstruct what must have occurred. In cases of latent pelvic tuberculosis it has been observed that endometrial tubercles are difficult to find in curettings obtained in the first half of the cycle and appear to be most numerous in curettings obtained just prior to menstruation. Furthermore, the location of such tubercles appears to be mainly in the superficial layers of the endometrium.[12] From these findings it has been assumed that the endometrial lesions are largely due to seedings from the tubal foci and that most of them are cast off with the menstrual slough, only to undergo redevelopment during the following cycle by the same process. The endometrial infection, however, is not entirely derived from the tubes, since it may persist after bilateral salpingectomy, probably because of lesions present in the deeper layers. Nevertheless, menstruation with its periodic disposal of the more heavily infected superficial portion must serve to slow the tuberculous process in the endometrium. With the occurrence of uterine pregnancy this disease, first in the endometrium and then in the decidua, develops without interference and in addition may well involve the developing ovum. Such a process would certainly predispose to early spontaneous abortion. The rather volcanic activation of the tuberculous process can be ascribed to the marked physiological activity of the pelvic organs during this event. It is difficult to conceive of such a pregnancy proceeding to term unless it developed in an endometrium free from tuberculosis. Since this is true in 30 to 40 per cent of cases,[7, 8, 9] such a circumstance is by no means impossible and may explain the postpartum appearance of acute pelvic tuberculosis after delivery of a term pregnancy.

Although many of the patients among those collected from the literature[25, 27, 28] have run a course similar to those just described, others are mentioned in whom pregnancy proceeded to term, the flare-up of pelvic tuberculosis taking place in the postpartum period. Only one such patient has been observed at Bellevue Hospital. Her history is briefly as follows:

CASE 11.—(Bellevue Hospital No. 49087-46) Mrs. J. P., aged 30 years, Negro, para 0, gravida ii, was admitted to the chest service at Bellevue Hospital on Oct. 15, 1946, because of a right pleural effusion and a tuberculous lesion at the right apex of three months' duration. She had been quite well. She was in the sixth month of pregnancy and had noted dyspnea during this period and a weight loss of 20 pounds over the past few months. Her first pregnancy had resulted in an uneventful abortion at three and one-half months in 1940. During her stay in the hospital she ran a low-grade fever. She was treated with thoracentesis and bed rest. X-ray showed a right pleural effusion and a faint shadow at the right apex. Her pregnancy proceeded normally. On December 17 she was transferred to the obstetrical service because of mild irregular pains which subsided after 24 hours. Her temperature rose to 101° F. but after five days resumed its low-grade character. She went into true labor on Jan. 1, 1947, but made little progress in spite of the deep engagement of the head. After more than twenty-four hours of labor she was subjected to a low-flap cesarean section. A normal female child that weighed 2,840 grams was delivered. When the peritoneal cavity was entered, about 400 c.c. of turbid fluid was encountered. The parietal peritoneum was studded with small white tubercles. Numerous adhesions were present. The left tube was congested and thickened; its fimbriated end was closed and adherent to the sigmoid. The

right tube appeared normal. Biopsies were taken from the peritoneum and the uterus. These were reported as characteristic of tuberculosis. Unfortunately, the placenta was not examined microscopically.

The patient ran a stormy postoperative course which continued after her return to the chest service. In February, 1947, she was transferred to a sanatorium. She was readmitted on May 20, 1947, with abdominal distention and a fecal fistula in the cesarean scar. The chest was negative on x-ray. She died on June 3, 1947. No autopsy was obtained.

This patient differed in several respects from those in the previous group. Her pregnancy was marked by the development of a primary tuberculous pulmonary infection during the second trimester. By the time that secondary tuberculosis of the peritoneum and tubes had taken place by hematogenous dissemination, the uterine cavity had become obliterated, thus preventing infection of the decidua by the usual method of spread. The secondary tuberculous lesion was completely unsuspected until the abdomen was opened at the time of cesarean section. Although the pulmonary lesion healed, a marked exacerbation of the secondary lesion occurred post partum to which the patient eventually succumbed. It must be concluded that the course of the disease in this patient differs from that in the preceding group in the development of the secondary lesion during and not prior to pregnancy. One can speculate whether the removal of the uterus and adnexa at the time of the cesarean section might not have influenced the subsequent course.

Summary

The relationship of pelvic tuberculosis to pregnancy can be summarized briefly as follows: In the vast majority of instances this type of pelvic infection is associated with intractable sterility. This is not surprising in the clinically recognizable cases. There are, however, a large number of patients with subclinical or latent pelvic tuberculosis, in whom tubal patency can be demonstrated, and in whom pregnancy is potentially possible. Observation and follow-up of many such patients have resulted in only one proved case of uterine pregnancy which occurred soon after the recognition of an endometrial infection.[5]

That pregnancy can take place in such patients is borne out by the reports of a number of ectopic gestations discovered in tuberculous tubes. Even this type of gestation is much rarer than would be expected. The surgical interruption of such pregnancies gives rise to no postoperative complications. Three instances of such an association are described in this report.

There appears to be a strong probability that uterine pregnancy can also occur on rare occasions in the presence of such a tubal lesion. The evidence for this, except in one case, is largely indirect. Five such cases are described, all terminating in early abortion with an abrupt exacerbation of the pelvic infection. In 4 of the 5 there is presumptive evidence that the primary tuberculous infections preceded pregnancy by more than a year. A sixth patient is described in whom the evidence points to the development of tuberculous salpingitis and peritonitis during pregnancy. She also developed an acute exacerbation of the infection in the postpartum period. Unlike ectopic pregnancy, the occurrence of uterine pregnancy in association with a pelvic tuber-

culous infection appears to be a very dangerous complication leading to an acute flare-up of pelvic peritoneal disease, sometimes to hematogenous spread of tuberculosis, and often to a fatal termination (3 of 6 cases).

Conclusions

1. Pelvic tuberculosis in women almost always causes sterility and this may be the only symptom of its presence in the subclinical stage of the infection.

2. In many patients with pelvic tuberculosis the disease is subclinical in form and the oviducts are patent.

3. In such patients ectopic pregnancies have been reported and to these three instances are added. The surgical treatment of such patients is not marked by untoward complications.

4. Cases have been reported, and to these five are added, which suggest that uterine pregnancy is possible under these circumstances. They terminate in early abortion complicated by acute exacerbation of the pelvic infection, often with a fatal termination.

5. Uterine pregnancy can be regarded as a serious complicating factor if pelvic tuberculosis is present.

6. In the rare event that uterine pregnancy should occur in a recently recognized case of pelvic tuberculosis, radical removal of the pelvic organs prior to abortion might be seriously considered.

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THE PREGNANT DIABETIC PATIENT*

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SINCE the discovery of insulin, there has been a marked alteration in the picture of diabetes and pregnancy. Infertility, increased incidence of abortions, and a high maternal mortality rate in diabetic women are now problems of the past. The present-day management of the pregnant diabetic patient is aimed at the reduction of the high fetal mortality, so that it approaches that of the nondiabetic patient. One group hopes to accomplish this by a correction of a hormonal imbalance, whereas the other feels that hormone therapy has little if any value. Likewise, the best method to effect delivery is still controversial. Unfortunately, there is no accurate figure representative of the present-day fetal loss, in order to compare the end results of the different schools of treatment.

The loss of viable fetuses, as reported in the past five years, varies from 10 to 45 per cent,[1-18] with the majority[4-18] reporting a loss greater than 15 per cent. Closer analysis reveals, however, that those reporting the highest fetal salvage include only recent cases, whereas the others generally include cases not only of the early insulin era, but even prior to the availability of insulin. Therefore, in comparing the fetal salvage of different schools, one must not only compare cases of similar severity, but also of the same era.

TABLE I. END RESULTS OF 246 PREGNANCIES IN DIABETIC PATIENTS AT THE JEWISH HOSPITAL OF BROOKLYN FROM 1932 TO 1953

OUTCOME	NO. OF PREGNANCIES		FETAL LOSS		PER CENT FETAL LOSS	
	1932-1949	1950-1953	1932-1949	1950-1953	1932-1949	1950-1953
Previable (under 1,000 grams):						
Spontaneous abortion, early	18	2	18	2	100.0	100.0
Spontaneous abortion, late	3	3	3	3	100.0	100.0
Therapeutic abortion	6	0	6	0	100.0	100.0
Viable (1,000 grams or more)	141	73	31	6	22.0	8.2
Total abortions	32		32		100.0	
Total viable	214		37		17.3	
Grand total	246		69		28.0	

Material

In order to evaluate the present-day fetal risk, all pregnancies of diabetic women delivered at the Jewish Hospital of Brooklyn since 1932 were reanalyzed. There were a total of 214 viable pregnancies, with a fetal loss of

*Presented at a meeting of the Brooklyn Gynecological Society on Oct. 21, 1953.

17.3 per cent (Table I). When this is divided into those delivered prior to 1950, however, and since then, a markedly different picture emerges. In the earlier period, the loss of viable fetuses was 22 per cent. This publication reports the results obtained in our more recent group, and the factors responsible for the reduction of the fetal loss to 8.2 per cent. This latter figure is a more representative index of the fetal mortality to be expected today.

Material

Seventy-eight pregnancies in diabetic patients were observed from Jan. 1, 1950, to Dec. 31, 1953 (Table I). Of these, 5, or 6.4 per cent, terminated in spontaneous abortions, and 73 were viable. The loss of viable fetuses was 8.2 per cent. There was no maternal mortality. In order to attain uniformity of recording, these cases were classified according to White (Table II). Of those with viable pregnancies, 37 per cent had severe diabetes (Classes C and D), with a fetal loss of 3.7 per cent; whereas in the milder cases of diabetes (Classes A and B), the fetal loss was 10.9 per cent.

TABLE II. FETAL LOSS IN 73 VIABLE PREGNANCIES IN DIABETIC WOMEN BY GROUP (1950-1953)

GROUP	NO. OF CASES	INTRAUTERINE DEATHS	STILLBIRTHS	NEONATAL DEATHS	PER CENT FETAL LOSS
A	2	0	0	0	0.0
B	44	3	0	2	11.4
C	24	0	1	0	4.2
D	3	0	0	0	0.0
E	0	0	0	0	0.0
F	0	0	0	0	0.0
Total	73	3 (4.1%)	1 (1.4%)	2 (2.7%)	8.2

Seven patients in this series received hormone therapy, either estrogen alone, or in combination with progesterone. One of the 6 fetal deaths occurred in the hormone-treated group.

Prenatal Care

Adequate prenatal care implies full cooperation of the internist, obstetrician, and patient, working as a team, and is responsible for the reduction of fetal loss in utero.

The patient should be seen at weekly intervals, throughout pregnancy, or even more frequently if necessary. A survey of the cardiovascular system, including ophthalmoscopic examination should be routine. Kidney function tests are indicated in long-standing cases of diabetes, and those with albuminuria. An x-ray of the abdomen should be taken, in order to detect the presence and degree of calcification of the uterine vessels.

Diets and insulin requirements are individualized, to satisfy the nutritional and metabolic requirements of the patient. Caloric values have varied between 1,000 and 3,000 or more, the obese receiving relatively less than the underweight patient. Common to all diets were a high protein, ranging between 1 to 2 Gm. per kilogram of bodyweight with a low sodium content. A low fat principle is followed and the remaining calories are supplied by carbohydrate.

At present, NPH appears to be the most appropriate type of insulin, in the majority of cases. However, protamine zinc insulin, or mixtures have been used with equally good results.

The patient is instructed to test the urine daily for acetone[5] in addition to sugar. This test will reveal early chemical or subclinical ketoacidosis and, with prompt recognition and appropriate treatment, will prevent the onset of clinical

acidosis. Ammonium chloride is used when edema occurs. Meticulous prenatal care will also tend to decrease the incidence of pre-eclampsia, and leads to its early recognition and prompt treatment.

Complications

Acidosis was the most common complication (Table III). It occurred in 21, or 28.7 per cent of the cases. It was responsible for 3 intrauterine deaths, and was a contributing factor in a neonatal death which occurred shortly after delivery. In the latter, the patient was admitted to the hospital for acidosis, and stated that she had experienced no fetal movements for 18 hours. In the presence of a good fetal heartbeat, immediate cesarean section was performed, with delivery of a moribund infant.

TABLE III. COMPLICATIONS OF PREGNANCY AND DELIVERY IN 73 VIABLE PREGNANCIES IN DIABETIC PATIENTS

COMPLICATION	NO. OF CASES	FETAL LOSS	PER CENT FETAL LOSS
Acidosis	19	4	21.1
Acidosis and pre-eclampsia	2	0	0.0
Pre-eclampsia alone	8	0	0.0
Polyhydramnios	3	0	0.0
Erb's palsy	2	0	0.0
Cerebral hemorrhage	1	1	100.0
Premature separation of placenta	1	1	100.0
None	37	0	0.0
Total	73	6	8.2

The high incidence of ketoacidosis, reported in this series and by others, can be explained in large measure by poor patient cooperation. This is best exemplified in 2 cases where the patients informed the physician of their intent to abandon their diabetic regime, with resultant acidosis and fetal death. One of these patients was a graduate nurse.

Pre-eclampsia was present in 10, or 14.9 per cent, of the cases. It occurred prior to the thirty-sixth week in 3 instances (Table IV). There was no fetal loss due to pre-eclampsia. The high fetal salvage in this group may be attributed to the prompt termination of viable pregnancies. Seven were terminated by the abdominal route, one of these following failure of induction by rupture of the membranes. In 2 cases labor was successfully induced and in one it occurred spontaneously.

TABLE IV. MODE OF TERMINATION OF PREGNANCY IN 10 CASES COMPLICATED BY TOXEMIA

METHOD OF TERMINATION	WEEK OF GESTATION							
	32	33	34	35	36	37	38	TOTAL
Cesarean section	1	0	0	1	1	3	0	6
Spontaneous labor	0	0	0	0	0	0	1*	1
Induced rupture of membrane	0	0	1	0	1	0	0	2
Failure of induction—cesarean section	0	0	0	0	0	1	0	1
Fetal loss	0	0	0	0	0	0	1*	
Total	1	0	1	1	2	4	1*	10

*Traumatic breech delivery.

Conservative management of toxemia with a viable fetus has proved costly, and is indicated only in nonviable pregnancies. A viable infant does better in a nursery incubator than in the mother's toxic environment.

Polyhydramnios occurred in 3 cases, and was not associated with any fetal abnormalities or loss.

Obstetrical Management

The obstetrical problem is (1) when, and (2) how to terminate pregnancy.

Time of Termination.—

Experience has shown that the risk of intrauterine fetal death increases greatly as the pregnancy approaches term. The risk prior to the thirty-sixth week is small and rises sharply thereafter. Since 1932, there have been sixteen intrauterine deaths, 14, or 87.3 per cent, occurring after the thirty-fifth week of gestation (Table V). It appears, therefore, that patients without complications should be delivered by the thirty-seventh week. Recurrent episodes of ketoacidosis and/or preeclampsia demand even earlier termination.

TABLE V. TIME OF OCCURRENCE OF 16 INTRAUTERINE DEATHS IN 214 VIABLE PREGNANCIES IN DIABETIC PATIENTS

WEEK OF GESTATION	NO. OF FETAL DEATHS
34	1
35	1
36	6
39	3
40	4
42	1
TOTAL	16

Mode of Termination.—

In the absence of cephalopelvic disproportion, pelvic delivery at the thirty-seventh week, or earlier, may be accomplished, if labor commences spontaneously, or follows induction. Labor started spontaneously in 22 cases, and was successfully induced in 5 others (Table VI).

Cesarean section is indicated if labor does not progress satisfactorily or if midpelvic-plane arrest occurs in the second stage. Prolonged labor or traumatic delivery[5-7] is attended by a high fetal mortality. There were 3 traumatic deliveries, 1 a breech, with death occurring within 24 hours postnatally, and 2 cases with impaction of the shoulder, resulting in Erb's palsy.

There was one instance of premature separation of the placenta, in the twenty-ninth week of gestation, with intrapartum death of a fetus with multiple congenital anomalies.

TABLE VI. MODE OF DELIVERY IN 73 VIABLE PREGNANCIES IN DIABETIC PATIENTS

TYPE OF DELIVERY	NO. OF CASES	INTRAUTERINE DEATHS	STILLBIRTHS	NEONATAL DEATHS	PER CENT FETAL LOSS
Spontaneous	11	2	1	0	27.3
Low forceps	8	0	0	0	0.0
Midforceps	7	0	0	0	0.0
Breech	1	0	0	1	100.0
Cesarean section	46	1	0	1	4.3
Total	73	3	1	2	8.2

Since a ripe cervix will rarely be found at the thirty-seventh week of gestation, elective cesarean section becomes the procedure of choice in the majority of cases. Forty-six, or 63 per cent, of the patients were delivered by this method. This section rate is more than double that found in our series from 1932 to 1949. During this earlier period, the section rate was 29.8 per cent, and the fetal loss of 22 per cent was almost three times as great as

that of the present series. As noted in Table VII, 16, or 45.7 per cent, of the primary sections were performed because of either a previous fetal loss or traumatic delivery. Prior to the performing of an elective cesarean operation, an x-ray study should be made to rule out bony fetal abnormalities.

On the day of the operation or delivery, no prolonged or intermediary acting insulin is given. An intravenous infusion of 1,000 c.c. of 5 per cent glucose in distilled water is started in the operating room, prior to the administration of the anesthesia, usually fractional spinal or occasionally local infiltration. When the incision is made, unmodified insulin is given either subcutaneously or added to the infusion, in the ratio of 1 unit for every 3 Gm. of glucose.

TABLE VII. INDICATIONS FOR CESAREAN SECTION IN 46 CASES

INDICATION	NUMBER OF CASES	
Repeat section	11	
Primary section	35	
Previous fetal loss		13
Previous traumatic delivery		3
Acidosis and/or pre-eclampsia		6
Primiparity		13
Total	46	

At the completion of the operation, the indwelling catheter is left in situ, and is of great aid in the management of the diabetes during the first 24 hours following operation.

In labor cases, oral feeding is withheld, and the patient is given a slow continuous intravenous infusion of 5 per cent glucose in water, not to exceed 3,000 c.c. in twenty-four hours, and is covered by unmodified insulin in a ratio of 1 unit of insulin to 3 Gm. of glucose.

During the first few days following delivery, there is usually a decrease in the insulin requirement, and an uncertain dietary intake. Regulation of the diabetes, therefore, during this interval, is best effected by the use of unmodified insulin, the dose being determined by fractional urine examinations. In a relatively short time thereafter, with stabilization of the metabolic state, the patient is placed on prolonged, or intermediary acting insulin.

Care of the Newborn

The newborn must be treated as premature, regardless of weight or gestational age, for their physiological development does not correspond to their size.

Pediatric care commences in the delivery room, immediately following birth. It consists of:

(1) clearing of the upper respiratory passage ways,
(2) aspiration of gastric contents,
(3) postural drainage, and
(4) placement of the newborn in a humidified oxygenated incubator. This atmosphere not only may be prophylactic, but also is therapeutic in atelectasis, secondary to hyaline membrane formation.

Blood sugar determinations and administration of glucose are of little value, for hypoglycemia in the newborn in most commonly physiological and rarely, if ever, requires correction.

In view of the marked edema of most infants, oral feedings are withheld in all cases for 48 hours, and even longer in the more edematous babies. Feedings are then begun in the usual manner.

Classification and Severity of Diabetes

At present there is no universal agreement as to what constitutes severe diabetes during pregnancy. One group[7] utilizes the amount of insulin required as the index, and the other, the age of onset and duration of the metabolic disturbance. Since premature vascular aging is one of the sequelae of diabetes, from an obstetrical point of view, it is the location of the arteriosclerotic change that determines the severity.

There is unanimity of opinion that kidney damage, regardless of the cause, or marked sclerosis of the uterine vessels results in an increased fetal risk. Duration of the metabolic disturbance, therefore, determines the severity obstetrically, only if these changes are present. It then appears more feasible to divide all pregnant diabetic patients into two groups, depending upon the fetal risk involved—an unfavorable and a favorable one. The unfavorable group includes all cases with a poor prognosis for either the fetus the mother or both; and cases in which pregnancy might be contraindicated. The poor fetal prognosis is apparent in the patients with renal damage and sclerosis of the pelvic vessels. Generally the fetal risk is not as great in the latter as in the former. The maternal risk is increased with extensive retinopathy or marked coronary insufficiency.

The favorable group is composed of all other cases of diabetes, regardless of age of onset, duration, or insulin requirements. It is difficult to see how two cases of the same duration, but with different ages of onset, can be classified as one more severe than the other. Likewise, the variation in insulin requirements does not exemplify the severity of the diabetes during pregnancy, as it does in the nonpregnant state. It has been demonstrated[17, 19] that there is no significant difference in fetal salvage in insulin-treated patients and in those not requiring insulin for control.

The fetal risk is increased in the favorable group with the development of ketoacidosis. This complication, in the absence of infection, is determined not by the duration of the disease, or the amount of insulin needed, but rather by inadequate medical supervision or poor patient cooperation. The patient's classification may change during the course of pregnancy, especially if albuminuria appears during the first two trimesters, indicative of impairment of kidney function.

This simplified classification, based upon fetal risk, is borne out, not only in the present series, but also in all our cases from 1932 to date (Table VIII). There was no significant difference in fetal mortality in Groups B, C, and D. Analysis of Nelson, Gillespie, and White's[1] results reveals similar findings.

Hormone Therapy

The reporting of more than 3,000 viable pregnancies in diabetic patients[1-18] in recent years, with a marked reduction in fetal and maternal mortality rates from the high levels characteristic of the preinsulin era, demonstrates conclusively the value of insulin in these individuals.

Although there is universal agreement as to the benefits of the pancreatic hormone, the efficacy of the ovarian hormones, estrogen and progesterone, in pregnancy in the diabetic patient is still debatable.

TABLE VIII. FETAL DEATHS IN 214 PREGNANCIES IN DIABETIC PATIENTS CLASSIFIED BY DIABETIC GROUPS, 1932-1953

GROUP	NO. OF CASES	INTRAUTERINE DEATHS	STILLBIRTHS	NEONATAL DEATHS	PER CENT FETAL LOSS
A	2	0	0	0	0.0
B	124	7	8	5	16.1
C	74	7	3	4	18.9
D	11	1	0	1	18.2
E	2	1	0	0	50.0
F	1	0	0	0	0.0
Total	214	16 (7.5%)	11 (5.1%)	10 (4.7%)	17.3

Substitutional hormone therapy is based upon the work of Smith and Smith[20] in toxemia, and the exponents of this therapy in the diabetic patient claim the following advantages:

1. It reduces the abortion rate to that of patients without diabetes.
2. It decreases the incidence of premature labor and pre-eclampsia.
3. It prevents premature placental senescence.
4. It increases the fetal salvage.

Other investigators,[21-24] however, have failed to conform the work of the Smiths in toxemia. Likewise many[25-28] have shown in controlled series in normal patients that the incidence of abortion, pre-eclampsia, and premature labor is identical in the stilbestrol-treated and control groups. Furthermore, the abortion rate and the incidence of premature labor in non-endocrine-treated series of pregnancies in diabetic patients are similar to those in the nondiabetic.

It has been demonstrated[29, 30] that prematurely delivered babies of stilbestrol-treated patients are larger than expected, and that the placentas of these pregnancies show premature placental maturation. Both of these effects are undesirable in the pregnancy of a diabetic patient.

Furthermore, the need for hospitalization in all the endocrine-treated diabetic patients[1] from the thirty-fourth week of gestation on is difficult to understand, if acidosis and pre-eclampsia are no problems.

Other investigators,[9, 17, 31-33] using hormone therapy, have failed to duplicate the excellent results reported by White, and their fetal loss is much greater than in the non-endocrine-treated series, and almost that of the pre-insulin era.

Several non-hormone-treated series[2, 3] have now been reported, in which the fetal loss is similar to that of the endocrine-treated group. The high fetal salvage (91.8 per cent) reported herein can be attributed to the following: (1) more adequate prenatal care, (2) increased, but still not ideal, patient co-operation, (3) premature delivery at the thirty-sixth or thirty-seventh week, or earlier, if necessary, and (4) liberalization of the use of cesarean section.

Since these factors are operating even more ideally in the White cases, it is difficult to see how the advocates of this therapy attribute their high fetal salvage in good part to substitutional hormones. To prove the validity of hormone therapy, a controlled series of pregnant patients with diabetes of equal severity should receive identical injection therapy, one of the hormone, the other of a placebo. The patients should be managed by the same group of physicians, and the knowledge of which patients are receiving the inert sub-

stance should be known only to the biostatistician connected with the project. Thus one would, to a great degree, eliminate the personal element on the part of the physician or patient.

At present it appears that substitutional hormone therapy is of little, if any, value.

Comment

The pessimism expressed by Oakley,[17] that good control of the maternal diabetes will not lower the fetal mortality below 23 per cent, cannot be shared by us and other workers in this field.

Since the turn of the present decade, the fetal loss in our institution has been reduced from 22 to 8.2 per cent. This marked reduction is significant and indicative of improved care.

Analysis of the fetal loss, however, reveals that 5 of the 6 fetal deaths could be termed preventable. Employment of elective cesarean section for a breech, instead of vaginal delivery, probably would have resulted in a more favorable end result for the infant. In the total series since 1932, there were 5 vaginal breech deliveries. Four infants were lost as a result of traumatic delivery, and the fifth, although surviving, had a bilateral Erb's palsy. This fetal loss of 80 per cent in breech delivery indicates elective cesarean section as the procedure of choice in these cases regardless of parity.

Late recognition of the diabetes and lack of patient cooperation were responsible for the 4 other preventable deaths. In one of these, glucose was first detected in a postprandial urine specimen following disappearance of the fetal heart sounds during the thirty-sixth week of gestation, and the diagnosis of diabetes was subsequently confirmed by a glucose tolerance test.

It should be routine in all patients to examine postprandial rather than the morning urine collected before breakfast. This will lead to earlier recognition of the unknown case of diabetes. Thus obstetricians will be actively engaged in diabetes detection at every office hour. Whereas the prebreakfast urine may be negative in many early and unsuspected cases of diabetes, the urine voided 2 hours after breakfast will reveal glycosuria in these cases. Sugar in the urine warrants prompt employment of a postprandial blood sugar determination, or a glucose tolerance test. A postprandial blood sugar value of 150 mg. per cent or over, taken one hour after breakfast, indicates a disturbance in carbohydrate tolerance. A value of 180 mg. per cent or above is definitive evidence of diabetes. Values between 150 and 180 mg. per cent are suggestive of diabetes, but confirmation should depend upon the performance of a glucose tolerance test. Although this routine will discover more cases of preclinical diabetes or evidence of a disturbed carbohydrate metabolism, nevertheless, the increased fetal salvage in the unrecognized case of diabetes will be more than an ample reward for the inconvenience caused the majority of patients subjected to this procedure.

Glucose tolerance tests should also be performed on all patients with unexplained intrauterine death, or excessive-sized infants, 4,000 grams or more. An excessive-sized infant delivered from a toxemic mother points strongly to the coexistence of unsuspected diabetes. Its presence was confirmed in 3 recent cases by glucose tolerance tests.

In this series, 10 patients developed diabetes during the course of pregnancy. Four of the infants in this group were lost, a mortality rate of 40 per cent. This represents two-thirds of our total fetal loss. Recurrent episodes of chemical or clinical ketoacidosis as a result of either poor control or lack of early diagnosis are probably responsible for this poor fetal salvage. Although published data reveal that fetal risk in the patient, with latent diabetes (Class A)[1] does not differ from that of the nondiabetic patient, nevertheless the fetal loss is not as small as it would appear. Experience[3, 5, 19] has shown that the increased loss commences prior to the development of clinical diabetes and may be as high as 20.5 per cent.

To increase the fetal salvage still further, a comprehensive program of education of both the laity and the profession is essential. Both the diabetic patient and the physician must know what constitutes adequate prenatal care, for the fetal loss is directly proportional to the management. The patient should be made aware, even prior to pregnancy, that a good fetal prognosis is also dependent upon her cooperation. Adequate medical care without patient cooperation results in a decreased fetal salvage. This is reflected in the literature by the higher fetal loss reported by investigators working with clinic patients, in contrast to those in a private series. At present elective cesarean section is the procedure of choice to effect delivery in the majority of diabetic patients. When methods of prevention of premature placental senescence are known, this may be replaced by vaginal delivery, except for obstetrical indications.

Summary and Conclusions

1. This series is composed of 73 viable pregnancies in diabetic patients since 1950, with a perinatal loss of viable fetuses of 8.2 per cent.

2. The abortion rate of 6.4 per cent was well within the normal limits for the nondiabetic.

3. A program of what constitutes adequate prenatal management is given. This is responsible for the increased fetal salvage during the intrauterine period.

4. Ketoacidosis is the prime factor responsible for fetal death in utero. This complication can be recognized in its chemical phase by the routine daily testing of the urine for acetone. Prompt recognition and therapy prevent clinical acidosis.

5. Pre-eclampsia with a viable fetus is best managed by prompt termination of pregnancy. This is responsible for the good fetal end result in the toxemia cases in this series.

6. Elective cesarean section is the procedure of choice to effect delivery in the majority of cases. The increased use of this procedure in this series (63 per cent), as compared to 29.8 per cent prior to 1950, has been accompanied by a sharp decline in fetal mortality from 22 to 8.2 per cent at present.

7. Delivery should be effected between the thirty-sixth and thirty-seventh weeks, and even earlier, if recurrent episodes of ketoacidosis or pre-eclampsia are present.

8. The newborn should be treated as premature, regardless of weight or gestational age.

9. A new classification of pregnant diabetic patients is proposed, based upon the obstetrical risk involved. This consists of two groups, a favorable and an unfavorable one. It is determined by the presence or absence of the sequelae of long-standing diabetes, which increase either the fetal or maternal risk, or both.

10. The value of substitutional hormone therapy is still questionable, and must await the results of controlled series.

11. The routine examination of postprandial, rather than prebreakfast, urine specimens by the obstetrician on all patients will lead to the earlier detection of the unsuspected case of diabetes.

12. The most important factor in further decreasing the fetal loss is education of both the laity and the profession as regards adequate prenatal care. Adequate care, without full patient cooperation, leads to a decreased fetal salvage.

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THE VALUE OF URINARY PREGNANEDIOL DETERMINATIONS AS AN INDICATION FOR THE USE OF PROGESTERONE IN THE TREATMENT OF THREATENED ABORTION*

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THE present status of the therapy of threatened abortion as reported from most clinics leaves a great deal to be desired.[1] Several methods of management have been employed but as yet no one drug, hormone, vitamin, or other therapeutic agent has produced any increased fetal salvage over that obtained from the use of bed rest and sedation alone.[1] An apparent increased fetal salvage has been reported by Smith[2] using stilbestrol in small upgraded doses but this has been challenged by several investigators[3-6] as probably being due to chance alone. Guterman and Tulsky[7] have reported favorably on progesterone when used in large doses in treating threatened abortion but their salvage rate is not much better than the spontaneous rate of cure of 50.0 per cent as postulated by Eastman.[8] Colvin and associates[9] de-emphasize the use of progesterone and report a salvage rate of 72.0 per cent in 1,570 cases in which there was no hormonal therapy at all. King,[1] in a recent review, showed salvage rates from several sources ranging from 40 to 87 per cent.

In a previous publication by one of us (W. S. B.),[10] a rational approach to this therapeutic problem was suggested. The assumption has been previously made that only about 4.0 per cent of all cases of threatened abortion could possibly benefit from progesterone therapy during the acute stage.[9] If these few cases could in some manner be singled out, it would greatly simplify management and would allow the attending physician to be reasonably certain that progesterone therapy would be of some value. Its use would be logical under such circumstances and not merely a drain on the finances of the patient. Our rationale of suggested treatment was first to determine if the conceptus was living as reflected by any dependable test for chorionic gonadotropic hormone and then to give progesterone only to those patients with a low urinary pregnanediol value. We accordingly began a controlled study in November, 1951, on the value of urinary pregnanediol determinations as an indication for progesterone therapy of threatened abortion. The results of treatment of all cases considered eligible for the study and admitted to this hospital between Nov. 1, 1951, and Nov. 1, 1953, make up the basis for this report.

*This work is not to be construed as necessarily reflecting the views of the Department of the Navy.

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Material

During the period from Nov. 1, 1951, to Nov. 1, 1953, 548 patients with the over-all diagnosis of abortion were admitted to our hospital for treatment. Of this number, 144 were threatened abortions as determined by the criteria of spontaneous onset of uterine contractions and bleeding from the uterus prior to the twentieth week of gestation without any actual passage of the products of conception. This resulted in an incidence of threatened abortion of 26.3 per cent. Only 57 cases, however, were considered to be eligible for the study. The remaining 87 cases were actually incomplete abortions at the time of the initial hospital examination, the patients had a negative frog test, or had received some type of hormonal therapy prior to admission, and thus these cases could not be used.

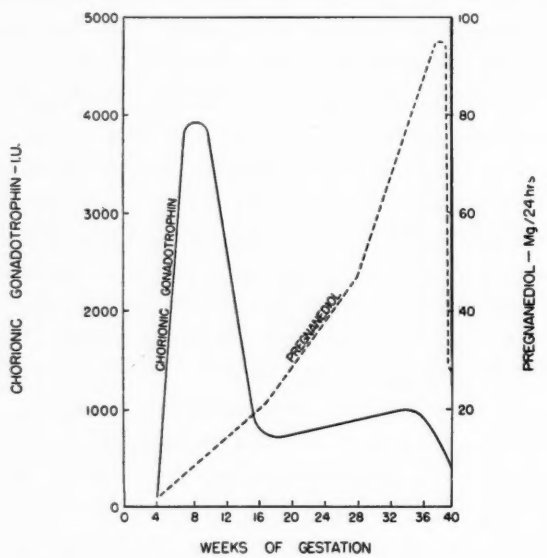

Fig. 1.—The average urinary excretion of chorionic gonadotrophin and pregnanediol glucuronidate during normal pregnancy. (From Swyer.[11])

Method

It has been contended by several investigators[11, 12] that the major product of progesterone metabolism is sodium pregnanediol glucuronidate. This substance can be demonstrated in the urine during the luteal phase of the menstrual cycle, during pregnancy, and during certain pathological conditions of the ovary. There is no apparent increase in the amount of pregnanediol in the urine during the first month of pregnancy but it begins to rise steadily from the fourth to the thirty-sixth week, when it attains its peak value of about 90 mg. per 24 hours and then rapidly drops off altogether immediately following delivery. Fig. 1 illustrates the rise of pregnanediol glucuronidate during pregnancy in contrast to chorionic gonadotropin which noticeably drops precipitously after the fourteenth week.

Based upon the assumption that sodium pregnanediol glucuronidate as found in the urine reflects the major portion of progesterone metabolism in the host, we collected a 12 hour urine sample from every patient with a positive male frog test for pregnancy at the time they were threatening to abort and had it analyzed for its sodium pregnanediol glucuronidate content.

TABLE I. COMPILATION OF ALL CLINICAL AND LABORATORY DATA OF ALL CASES STUDIED IN SERIES

CASE NO.	GESTATION WEEKS ON ADMISSION	URINARY PREGNANEDIOL VALUE PER 24 HOUR SPEC.		TREATMENT*		PREGNANEDIOL LEVEL CLASSIFICATION	RESULT OF RX AS OF NOVEMBER 1, 1953†	
		ADMISSION	DISCHARGE	IN HOSP.	OUT OF HOSP.			
1	19	11.88	8.00	P	P	Low	D	7 pounds
3	10	0 mg.	1.62	P	P	Low	A	12 weeks
4	20	12.4	5.92	P	P	Low	D	Term
5	16	0 mg.	4.92	S	S	Low	D	2 pounds, 11 ounces
6	7	2.04	2.8	S	S	Low	D	8 pounds, 3 ounces
7	12	0 mg.	.78	N	N	Low	D	5 pounds, 8 ounces
10	12	52.00	—	N	S	Normal	D	6 pounds, 6 ounces
13	13	5.14	—	N	N	Low	D	5 pounds, 14 ounces
14	11	7.60	—	N	N	Normal	A	12 weeks
15	11	28.94	18.86	N	S	Normal	D	1 pound, 14 ounces
16	14	0 mg.	—	P	P	Low	D	5 pounds, 10 ounces
17	19	39.2	—	N	N	Normal	D	6 pounds, 2 ounces
19	16	—	17.62	N	N	Normal	D	6 pounds, 8½ ounces
20	13	11.14	16.14	P	P	Normal	D	6 pounds, 5½ ounces
21	14	4.54	3.52	N	N	Low	D	7 pounds, 3 ounces
22	17	33.22	18.54	N	S	Normal	P	Term
25	14	14.40	—	N	N	Normal	D	8 pounds, 5 ounces
26	17	21.28	—	N	N	Normal	D	6 pounds, 9½ ounces
28	19	24.42	29.56	N	N	Normal	D	5 pounds, 2 ounces
30	9	27.22	32.88	N	N	Normal	D	7 pounds, 14 ounces
32	18	48.28	—	N	S	Normal	P	Term
33	14	23.12	—	N	P	Normal	A	17 weeks
34	10	15.44	—	P	P	Normal	D	Term
35	22	28.70	—	N	N	Normal	P	Term
36	9	30.28	20.60	N	S	Normal	A	11 weeks
37	11	24.92	24.28	N	N	Normal	A	11 weeks
39	14	46.46	—	N	S	Normal	A	18 weeks
40	12	29.20	40.64	N	S	Normal	D	6 pounds, 14 ounces
41	13	29.18	—	N	-	Normal	A	13 weeks
43	10	6.52	15.48	P	P	Normal	A	14 weeks
44	9	26.40	—	P	P	Normal	A	10 weeks
45	15	27.94	—	N	S	Normal	D	7 pounds, 7½ ounces
46	14	21.12	—	P	P	Normal	P	Term
47	11	14.14	16.84	P	P	Normal	D	4 pounds, 5 ounces
48	12	21.24	33.06	P	P	Normal	D	7 pounds, 10½ ounces
49	11	12.96	16.98	N	N	Normal	D	6 pounds, 2 ounces
51	10	8.06	19.90	P	P	Normal	P	Term
52	16	37.36	14.04	N	N	Normal	D	6 pounds, 8 ounces
53	9	50.04	—	P	P	Normal	A	10 weeks
54	16	16.86	24.48	P	P	Normal	P	38 weeks
55	13	25.12	27.04	P	P	Normal	A	19 weeks
56	10	35.20	42.02	P	P	Normal	P	37 weeks
57	8	21.38	—	P	P	Normal	P	35 weeks
59	11	11.86	—	N	N	Normal	D	9 pounds, 6 ounces
61	12	6.10	—	N	-	Low	A	12 weeks
64	18	23.08	21.54	P	P	Normal	P	Term
69	16	23.64	24.92	P	P	Normal	P	Term
72	18	24.48	—	N	N	Normal	D	7 pounds, 8 ounces
78	19	5.18	11.20	N	-	Low	A	20 weeks
79	11	2.76	—	N	-	Low	A	11 weeks
82	16	23.20	22.32	N	N	Normal	D	Stillborn
83	11	7.46	5.22	P	P	Low	P	38 weeks
85	22	37.14	20.24	P	P	Normal	P	30 weeks
89	7	9.16	10.86	P	P	Normal	P	26 weeks
90	11	13.06	25.68	N	N	Normal	P	20 weeks
95	14	32.30	—	P	P	Normal	A	22 weeks
105	14	8.12	—	P	P	Low	P	18 weeks

*P, progesterone.
S, stilbestrol
N, no hormonal therapy.
†D, delivered.
A, aborted.
P, pregnant.

Another 12 hour urine sample was collected in most instances in each salvaged case just prior to discharge from the hospital in order to have a more accurate value upon which to base our conclusions. The male frog *(Rana pipiens)* pregnancy test[13] was used exclusively in this study. This test has been reported as being 97.0 per cent accurate.[13] Following the urinary pregnanediol determination, the cases in the series were divided for treatment purposes into two main groups: (1) those with a normal excretion of the hormone; and (2) those with a value less than 50 per cent of the average amount normally excreted at a given stage of gestation in a 24 hour specimen of urine.[12] Each was again divided into another two groups, one-half receiving progesterone, 100 mg. daily either orally or parenterally, and the other half no hormone at all (two patients were inadvertently given stilbestrol as inpatients but were retained in the study). All patients were kept at bed rest until there had been no bleeding or cramping for forty-eight hours after which they were permitted to get up. If bleeding or cramping did not return after an additional twenty-four hours, they were discharged to the outpatient department for follow-up care on one of the following three methods of management: (1) the entire group receiving progesterone in the hospital was continued on progesterone orally, 100 mg. daily, until the twentieth week of gestation and then the dose was reduced 25 mg. daily each week until they were taking no hormone at all by the twenty-fourth week of pregnancy; (2) the group that received no hormonal therapy in the hospital was divided into two sections and one-half was discharged on no hormonal treatment; (3) the other half was sent home on stilbestrol in accordance with the recommendations of Smith.[2] Table I contains all the essential clinical and laboratory data on all eligible cases utilized in this study.

Chemical Method

All 12 hour urine specimens were analyzed for their sodium pregnanediol glucuronidate content by the spectrophotometric method, a modification of Guterman's test, as outlined by Fister.[14] The 12 hour value was then doubled to obtain the 24 hour excretion of pregnanediol by each patient. Fig. 2 contains all the urinary pregnanediol values of the cases studied in relation to the normal pregnanediol curve and the stage of gestation in weeks. This technique was standardized for accuracy by determining the urinary pregnanediol excretion on several known normal pregnant patients at various stages of pregnancy and the results then compared with the known normal pregnanediol excretion curve as reported by Swyer[11] (Fig. 1). Fourteen patients failed to excrete over 50 per cent of the average value anticipated at their stage of gestation and are therefore counted as low or subnormal as noted in Table I.[12] The remaining 43 patients excreted the average value of urinary pregnanediol or more than that anticipated at their stage of gestation and are recorded as normal.

TABLE II. TREATMENT RESULTS IN HOSPITAL IN RELATION TO URINARY PREGNANEDIOL LEVEL

METHOD OF TREATMENT	PREGNANEDIOL LEVEL		RESULTS OF TREATMENT	
	NORMAL	LOW	ABORTED	SALVAGED
Progesterone	18	6	0	24
No hormone	25	6	4	27
Stilbestrol	0	2	0	2
Total	43	14	4	53

Results of Treatment

During the period from Nov. 1, 1951, through Nov. 1, 1953, there were 57 patients with the diagnosis of threatened abortion admitted to the hospital who were eligible for use in this study. These cases were subdivided for treat-

ment as previously described and the results of treatment in the hospital in relation to the urinary pregnanediol level can be found in Table II. It will be noted that only 4 cases of the 57 aborted in the hospital and all were from the group that received no hormonal treatment, one with a normal pregnanediol level and 3 with a value less than 50 per cent of the accepted average level.

The 53 salvaged cases discharged to the outpatient department were divided into three groups as previously described. Twenty-five continued to receive oral progesterone through the twenty-fourth week of gestation and of this group 7 patients aborted, 6 with a normal urinary pregnanediol level and one with a low level. Eighteen patients who had received no hormonal therapy in the hospital continued on no hormonal treatment as outpatients. Two of these patients aborted, and both of them were in the normal pregnanediol group. Eight patients who had received no hormone in the hospital were given stilbestrol in accordance with the schedule of Smith[2] and of these only 2 aborted, both having normal pregnanediol levels. Forty-two patients either continued uninterruptedly in their pregnancies to date or have been delivered of living infants. Reference to Table III will reveal the results of treatment on the outpatient schedule in relation to the urinary pregnanediol level.

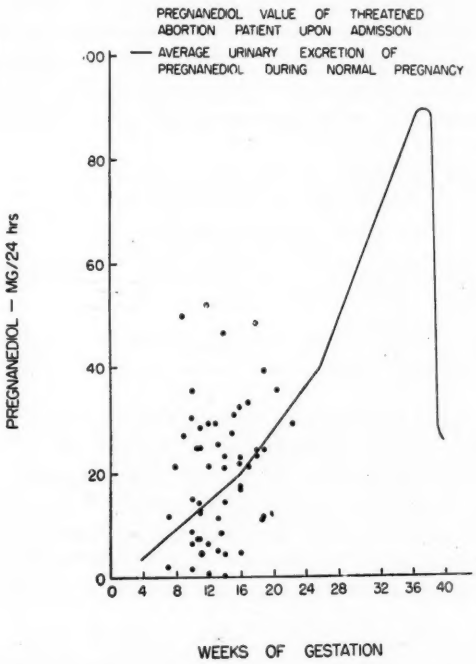

Fig. 2.—The urinary pregnanediol values of all threatened abortion cases utilized in this study.

Further analysis of the salvaged cases revealed 39 patients to have progressed beyond 28 weeks of gestation or to have delivered a viable infant and only 3 cases to be still in the previable stage. The greatest apparent response to treatment was noted in the group that received no hormone, with 88.8 per cent of 18 cases progressing beyond 28 weeks' gestation. The second best apparent salvage occurred in the stilbestrol-treated cases with 80 per cent of 10 cases retaining the pregnancy, all of which were beyond the stage of viability. Table IV contains the over-all treatment results in relation to the level of urinary pregnanediol.

TABLE III. TREATMENT RESULTS ON OUTPATIENT SCHEDULE IN RELATION TO URINARY PREGNANEDIOL LEVEL

METHOD OF TREATMENT	PREGNANDIOL LEVEL		RESULTS OF TREATMENT	
	NORMAL	LOW	ABORTED	SALVAGED
Progesterone	19	6	7	18
No hormone	15	3	2	16
Stilbestrol	8	2	2	8
Total	42	11	11	42

TABLE IV. OVER-ALL TREATMENT RESULTS IN RELATION TO URINARY PREGNANEDIOL LEVEL

METHOD OF TREATMENT	PREGNANEDIOL LEVEL		RESULT OF TREATMENT		
				SALVAGED CASES	
	NORMAL	LOW	ABORTED	UNDER 28 WKS.	OVER 28 WKS.
Progesterone	19	6	7	2	16
No hormone	16	6	6	1	15
Stilbestrol	8	2	2	0	8
Total	43	14	15	3	39

An analysis of the type of treatment in relation to the urinary pregnanediol level of the 15 patients who aborted is contained in Table V. It will be noted that only 4 patients with a low urinary pregnanediol level aborted. One was treated with oral progesterone and 3 received no hormonal therapy. The remaining 11 patients had normal pregnanediol levels. Six of these cases were treated with progesterone, 3 with no hormone, and 2 received stilbestrol.

TABLE V. ANALYSIS OF PATIENTS WHO ABORTED IN RELATION TO PREGNANEDIOL LEVEL AND TYPE OF TREATMENT

PREGNANEDIOL LEVEL	METHOD OF TREATMENT			TOTAL
	PROGESTERONE	NO HORMONE	STILBESTROL	
Normal	6	3	2	11
Low	1	3	0	4
Total	7	6	2	15

Table VI contains an analysis of the salvaged cases in relation to the type of treatment and the urinary pregnanediol level. It will be noted 30 of the 39 cases that are beyond 28 weeks' gestation are from the normal pregnanediol level group and 9 are from the subnormal group. Except for the 6 patients on stilbestrol, they are fairly evenly divided as to the three types of treatment received. Of 3 patients still under twenty-eight weeks' gestation, two are from the normal pregnanediol group, two received progesterone, and one, no hormonal therapy.

TABLE VI. ANALYSIS OF SALVAGED CASES IN RELATION TO PREGNANEDIOL LEVEL AND TYPE OF TREATMENT

METHOD OF TREATMENT	URINARY PREGNANEDIOL LEVEL				TOTAL
	NORMAL SALVAGED CASES		LOW SALVAGED CASES		
	UNDER 28 WKS.	OVER 28 WKS.	UNDER 28 WKS.	OVER 28 WKS.	
Progesterone	1	12	1	4	18
No hormone	1	12	0	3	16
Stilbestrol	0	6	0	2	8
Total	2	30	1	9	42

The expelled products of conception when recoverable and the tissue obtained by curettage in all the 15 aborted cases were examined microscopically

by the Department of Pathology. The pathological findings in relation to the level of urinary pregnanediol and the type of treatment in each case are tabulated in Table VII. Three patients with a low urinary pregnanediol level had no demonstrable defects in either the expelled secundines or the curettage specimen, while one specimen contained a macerated embryo. The remaining 11 patients had normal urinary pregnanediol levels. Six of these had findings consistent with a normally developed embryo and placenta, 3 revealed benign hydropic degeneration, one, findings suggestive of a blighted ovum, and one, advanced autolysis of the embryo. Thus it may be assumed that the normal urinary pregnanediol level in the 5 cases with demonstrable defects in the abortuses did not forecast an accurate prognosis as abortion was probably inevitable. This percentage of defects in the ova and placentas closely approximates the findings reported by Wall and Hertig,[15] based on their analysis of 100 abortuses.

TABLE VII. MICROSCOPIC PATHOLOGY OF ABORTED PRODUCTS OF CONCEPTION

ABORTED CASES	PREGNANEDIOL LEVEL	TREATMENT	MICROSCOPIC PATHOLOGICAL DIAGNOSIS
No. 2	Low	Progesterone	Late secretory endometrium.
No. 14	Normal	No hormone	Normal six weeks' placental tissue.
No. 33	Normal	Progesterone	Amniotic debris, blood, clot, blighted ova.
No. 36	Normal	Stilbestrol	Hydropic degeneration placenta.
No. 37	Normal	No hormone	Necrotic decidua, degenerated chorionic villi.
No. 39	Normal	Stilbestrol	Degenerated decidua; autolysis of embryo.
No. 41	Normal	No hormone	Normal fetus and placenta, 3½ months.
No. 43	Normal	Progesterone	Postabortal endometritis.
No. 44	Normal	Progesterone	Hydropic degeneration placental tissue; anencephaly.
No. 53	Normal	Progesterone	Hydropic degeneration placental tissue.
No. 55	Normal	Progesterone	Necrosis, decidual tissue.
No. 61	Low	No hormone	Infected decidual tissue.
No. 78	Low	No hormone	Partially necrotic placental and decidual tissue. Normal embryo, age 10 weeks.
No. 79	Low	No hormone	Necrotic decidual and placental tissue; macerated 6 weeks' embryo.
No. 95	Normal	Progesterone	Normal-appearing premature immature male infant, weight 1 pound, ½ ounce.

In our study at this time we have a total of 42 cases salvaged out of 57, for a relative percentage of 73.7 per cent and a standard error of percentage of 5.7 per cent. Thirty-nine of these cases, or 68.4 per cent, are beyond the stage of viability and 28 have delivered living infants, thus giving an absolute salvage rate of 49.1 per cent.

Comment

There were 57 cases of threatened abortion admitted to our hospital that were considered eligible for use in the pregnanediol series. Forty-three patients had a normal pregnanediol level and 14 were considered to be subnormal or low. Nineteen with a normal pregnanediol level were treated with progesterone and, of these, 6 patients aborted, yielding a salvage of 72.2 per cent. Of the 6 patients with a low pregnanediol level who received progesterone, only one aborted for a salvage rate of 83.3 per cent. Thus it would appear that progesterone therapy was unnecessary in the former group and may have increased the fetal salvage over that normally anticipated in the latter group. An analysis of the abortuses, however, revealed that 3 of the progesterone-

treated cases with normal pregnanediol levels would never have responded to therapy as the ova were developmentally defective and this fact was not revealed by a decreased output of pregnanediol in any case. Thus a normal pregnanediol level does not always assure a safe prognosis.

Twenty-five cases originally treated in the hospital by only bed rest and sedation had normal pregnanediol levels. Only one of these patients aborted for a salvage rate of 96.0 per cent. This perhaps supports the contention that any patient with a normal urinary pregnanediol level does not require progesterone therapy. Of the six patients with low pregnanediol levels who were treated with no hormone, 3 aborted for a salvage rate of only 50.0 per cent. An analysis of these abortuses did not reveal any developmental nor degenerative defects. It is postulated that progesterone therapy might have increased the fetal salvage if given to these patients.

Of the original 25 patients who received no hormonal therapy and had a normal urinary pregnanediol level, 15 were continued with no hormonal treatment as outpatients. Thirteen of these cases, or 86.6 per cent, were salvaged. Only one of the abortuses showed evidence of degeneration of the chorionic villi and thus might not have been salvageable by hormonal therapy if it had been given. The 3 pregnancies in patients with low pregnanediol levels treated as outpatients without hormones were all salvaged. Thus again it would appear that a normal pregnanediol level does not necessarily guarantee a safe prognosis in each case and probably is good evidence for not giving progesterone therapy in such cases. Also, a low pregnanediol level was no definite indication for progesterone therapy, as evidenced by our salvage of 3 cases out of 10 in the series that received no hormones at any time.

A small group of 10 cases, 8 with normal urinary pregnanediol levels and two with low levels, were treated as outpatients on stilbestrol in accordance with the recommendations of Smith.[2] Both cases with low pregnanediol levels were salvaged. Two patients with normal pregnanediol levels aborted and the remaining 6 cases or 75.0 per cent, were salvaged. An analysis of the abortuses, however, again revealed degenerative damage sufficient to prevent normal progressive growth of the embryo in either case despite the stilbestrol therapy. This, in effect, bears witness that stilbestrol or progesterone is of no benefit in such cases and probably should be withheld in the presence of a normal urinary pregnanediol level.

The best over-all salvage occurred in the outpatient group of 18 cases on no hormonal therapy with survival in 16 cases, or 88.8 per cent. The next best salvage was in the stilbestrol-treated group with 80.0 per cent, and the least response to treatment occurred in the 25 patients on progesterone with only 18 pregnancies surviving, for a rate of 72.0 per cent.

The over-all salvage of 42 cases, or 73.7 per cent, to date is considered to be comparable to results reported from other clinics[1] but our absolute salvage of only 39, or 68.4 per cent, is not much better than the anticipated spontaneous salvage rate of 50.0 per cent as postulated by Eastman.[8]

Summary and Conclusions

1. Fifty-seven cases of threatened abortion with a positive male frog test for pregnancy were selectively treated in our hospital utilizing progesterone, stilbestrol, or no hormone, following the analysis of a 12 hour urine specimen for the sodium pregnanediol glucuronidate level in each case.

2. There was a normal urinary pregnanediol level in 43 cases and it was reported as low or subnormal in 14 cases.

3. Fifteen patients aborted, for an incidence of 26.3 per cent. Eleven of these had normal urinary pregnanediol levels and in 4 cases they were reported as subnormal.

4. Eight of the aborted cases with normal urinary pregnanediol levels had received hormonal therapy but 5 of the abortuses subsequently proved to have degenerative or developmental defects inconsistent with normal progression of the pregnancy.

5. Three patients with low urinary pregnanediol levels received no hormonal therapy and aborted apparently normal products of conception. This represents 5.3 per cent of the total number of cases studied that might have been salvaged if given progesterone.

6. Forty-two cases were considered salvaged, for an incidence of 73.7 per cent. Thirty-nine of these cases, or 68.4 per cent, have progressed beyond 28 weeks' gestation and 28 patients have delivered living infants for an absolute salvage of 49.1 per cent.

7. The best salvage occurred in the group with no hormonal treatment with 16 cases, or 88.8 per cent. Fifteen of these are beyond 28 weeks' gestation.

8. The next-best salvage was noted to be in the stilbestrol-treated group with 8 cases, or 80.0 per cent, progressing beyond the stage of viability.

9. The least response to treatment occurred in the progesterone-treated group, with only 18 cases out of 25, or 72.0 per cent, salvaged.

10. The urinary pregnanediol determination when normal did not assure a safe prognosis for 5 of 15 patients who aborted in our study, for an incidence of 33.3 per cent of the abortuses and 8.7 per cent of the cases studied.

11. The urinary pregnanediol level when low did not indicate a poor prognosis in 3 cases out of 14 in our study despite the withholding of progesterone therapy.

12. From the results of this study to date, urinary pregnanediol determinations on the urine of patients threatening to abort have not materially improved fetal salvage either by accurately forecasting prognosis or by indicating a need for progesterone therapy.

13. The results of this study also suggest that progesterone therapy is not indicated in patients with a normal excretion of pregnanediol in the 24 hour urine and is of doubtful value where the urinary pregnanediol level is found to be subnormal.

We wish to express our sincere appreciation to Captain C. B. Galloway (MC) USN, Commanding Officer of the Naval Medical Field Research Laboratory, Camp Lejeune, North Carolina, without whose invaluable laboratory facilities this presentation would not have been

possible; to Drs. J. P. Baker, H. A. Claiborne, F. N. Dickman, J. G. Johnson, W. J. A. Ford, and G. W. Tucker, for their kind cooperation in the collecting of the case histories; and to Mrs. Gertrude R. Kuell, for her faithful assistance in the typing of this manuscript.

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COMPARTMENTAL DISTRIBUTION AND SHIFT OF WATER AND ELECTROLYTES IN PRE-ECLAMPSIA*†

Part II. A Comparison of the Effects of Isotonic and Hypertonic Solutions of Glucose When Administered Intravenously to Patients With Pre-eclampsia

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THE nature of the altered physiology present in the true toxemias of pregnancy is, as yet, unknown. Many clinical observations have been made, and many theories to explain these clinical observations have been proposed. Most of these theories pertain to the apparent water retention observed in these patients. There is little doubt that one of the first clinical manifestations of early or impending toxemia is an abnormal degree of water retention or a positive water balance. This is clinically apparent by a rapid weight gain, followed frequently by the development of edema. As the disease becomes more severe, there is frequently a pronounced hemoconcentration as manifested by an increased packed-cell volume and a decreased plasma volume. Freis and Kenny[1] studied the relationship between the plasma volume and the "available fluid" in normal and toxemic patients. They observed that the ratio of the two followed a specific pattern in normal pregnancy, but that in toxemic pregnancy this pattern was altered because the extracellular fluid volume increased out of proportion to the increase in plasma volume. They suggested that abnormal fluid distribution might be explained in part by a deficiency of total circulating proteins. Strauss[2] and others have attempted to explain the water retention and edema on this same basis. The time-honored rationale for intravenous glucose therapy as expressed by Dieckmann[3] is that hypertonic glucose solutions cause hemodilution with a resultant increase in urinary output. Dieckmann[4] further states that 5 or 10 per cent solutions of glucose are without beneficial effect, and in fact, tend, to produce an increase in total body water.

One of the stimuli for this investigation was the frequent clinical observation that a patient with severe pre-eclampsia and oliguria or anuria responded unfavorably to the intravenous administration of 5 per cent glucose solutions. The unfavorable response was usually manifested by an obvious increase in the amount of edema, and little or no commensurate increase in urinary output. Clinically, then, it was apparent that the vascular compartment had lost its

*Presented at the Twenty-first Annual Meeting of the Central Association of Obstetricians and Gynecologists, Houston, Texas, Nov. 5 to 7, 1953.

†Aided in part by the Edward G. Schlieder Educational Foundation of New Orleans, La.

capacity to attract and retain water. The extravascular compartment, on the other hand, had increased its potentiality for attracting and holding water. An attempt has been made in this investigation to evaluate the physiologic effects of 5 and of 20 per cent solutions of glucose in distilled water when administered intravenously to normal patients and to patients with pre-eclampsia.

Procedure

All patients included in this investigation were at complete bed rest for at least six hours prior to any procedure. They had received neither drugs nor food within this same interval of time. There had been, however, no restriction of water. An indwelling catheter was inserted into the bladder at the onset of the procedure to ensure accurate collection of the urine during each interval under investigation. The initial plasma-volume determination in each patient was done by means of the dye T-1824, as described in detail in a previous publication.[5] A flame spectrophotometer* was used for all determinations of sodium and potassium. Chlorides were determined by the method of Schales and Schales.[6]

The first phase of this program was concerned with the effects of 1,000 c.c. of a 5 per cent solution of glucose on the plasma and packed-cell volumes and on the compartmental distribution of water and electrolytes in normal and in pre-eclamptic patients. The second phase of this program consisted of a parallel study utilizing 20 per cent solutions of glucose. One direct plasma volume and three packed-cell volume determinations were made on each patient at specific times which were related to the intravenous infusion of the glucose solution. The *first* packed-cell volume and the only direct plasma volume determinations were done immediately prior to the beginning of the infusion. The *second* packed-cell volume determination was made 10 minutes after the infusion was completed, and the *third* one hour after the second. Throughout this study, the infusion of 1,000 c.c. of fluid was completed within a twenty-minute period. The thirty-minute interval beginning with the start of the infusion and ending with the determinations done ten minutes after the completion of the infusion, has been designated as interval I. The sixty-minute period following interval I, has been designated as interval II. The serum concentrations of sodium, potassium, and chloride were determined at the time of each packed-cell volume determination. The urine was quantitatively collected during each interval, and the content of sodium, potassium, and chloride of each sample was determined. The total circulating quantities of water, sodium, potassium, and chloride were calculated on a gram-weight basis at the beginning and at the end of each interval. Any *decrease* in these respective quantities within the vascular compartment which could not be accounted for by the urinary output were assumed to be due to a shift of water, sodium, potassium, or chloride from the vascular into the extravascular compartment. Similarly, any *increase* of one or more of these substances in the vascular compartment which could not be accounted for by the infused solution was interpreted as evidence that there had occurred a shift of one or more of these elements from the extravascular into the vascular compartment. By these calculations, intervals I and II represent short duration balance studies of the extravascular compartment with regard to water, sodium, potassium, and chloride as influenced by the rapid infusion of 1,000 c.c. of a 5 or a 20 per cent solution of glucose. The insensible losses of water and electrolytes were not included in these calculations because of the short duration of the study interval.

*Process and Instruments Company of New York, N. Y.

Results

Phase I. Isotonic Solutions of Glucose.—

Normal pregnancy: The means of the plasma and the packed-cell volume changes produced in 11 normal pregnant patients by the administration of 1,000 c.c. of a 5 per cent solution of glucose are illustrated graphically in Fig. 1.

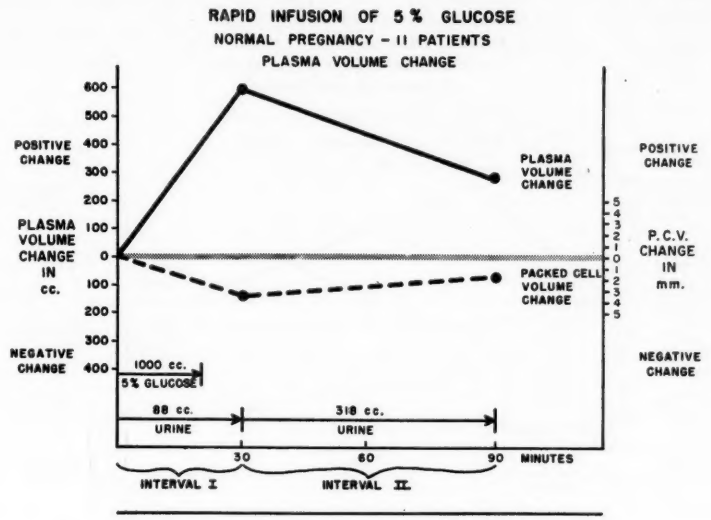

Fig. 1.

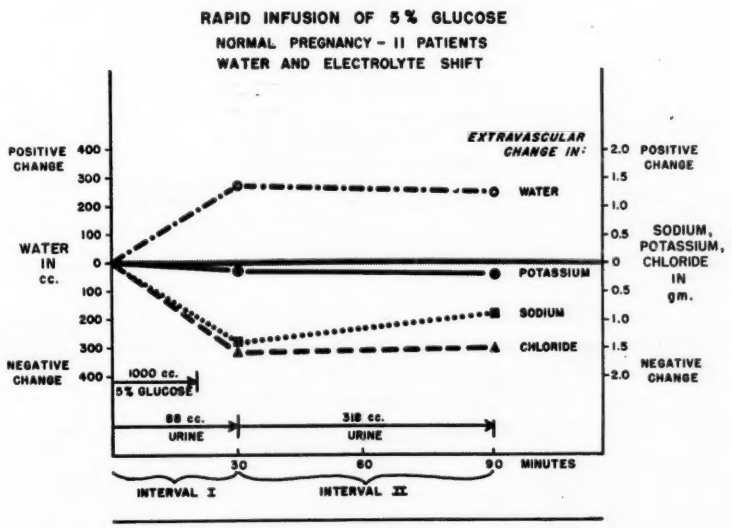

Fig. 2.

It is apparent that true hemodilution was produced during interval I, and that this hemodilution persisted to some extent for the entire period under observation. Fig. 2 illustrates the changes in the water and electrolyte content of the extravascular compartment. It can be seen that during interval I there occurred a shift of approximately 275 c.c. of water from the vascular into the extravascular compartment. This increase in extravascular water was main-

tained for the duration of interval II, thus producing a positive water balance in the extravascular compartment. There was a decrease of sodium and chloride within the extravascular compartment representing a shift of these elements from the extravascular into the vascular compartment. No significant shift in potassium was demonstrated. The loss of sodium and chloride by the extravascular compartment persisted but to a lesser degree during interval II. The total urinary output during intervals I and II was 406 c.c.

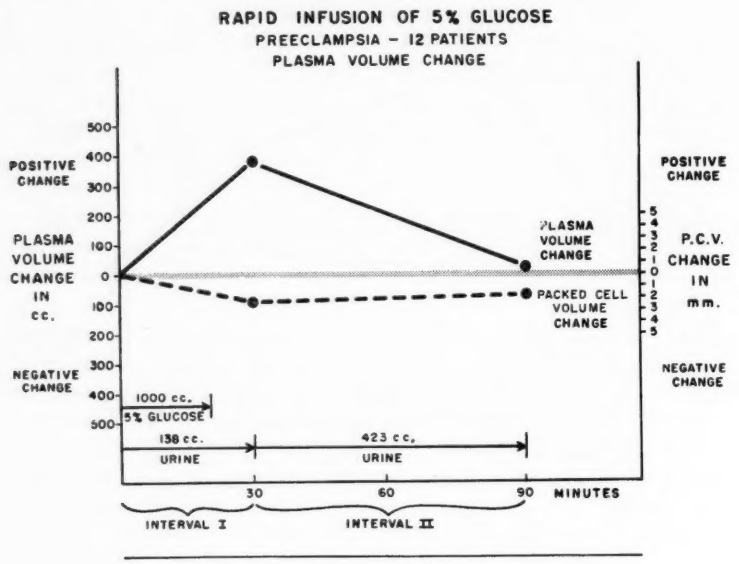

Fig. 3.

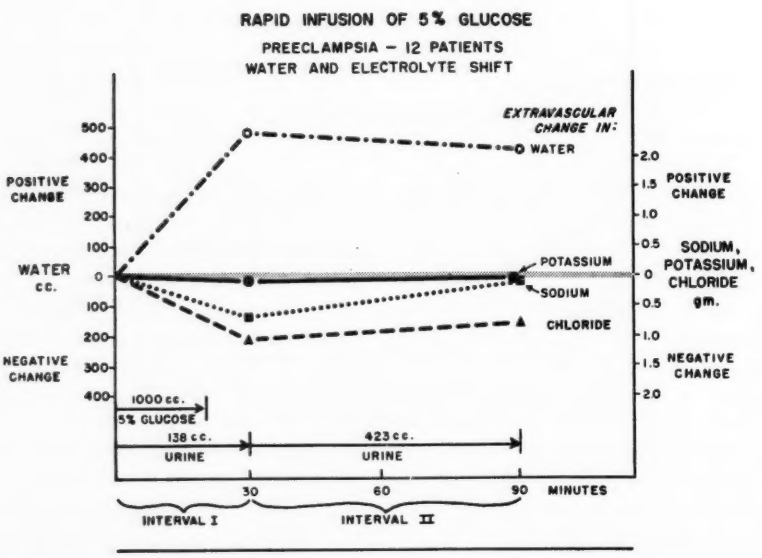

Fig. 4.

Pre-eclampsia: The effect of 1,000 c.c. of a 5 per cent solution of glucose administered intravenously to patients who had pre-eclampsia was determined as in the normal pregnant patients. Fig. 3 illustrates the mean changes in the

plasma and packed-cell volumes in 12 patients with pre-eclampsia. A true hemodilution was produced during interval I. During interval II, however, the plasma volume returned to its preinfusion level. Fig. 4 illustrates the changes in water and electrolyte content of the extravascular compartment in these same 12 patients with pre-eclampsia. During interval I, there was a gain of approximately 480 c.c. of water by the extravascular compartment. There was a loss of sodium and of chloride by the extravascular compartment. A rapid shift of water was demonstrated to have occurred from the vascular into the extravascular compartment. During interval II, a slight decrease occurred in

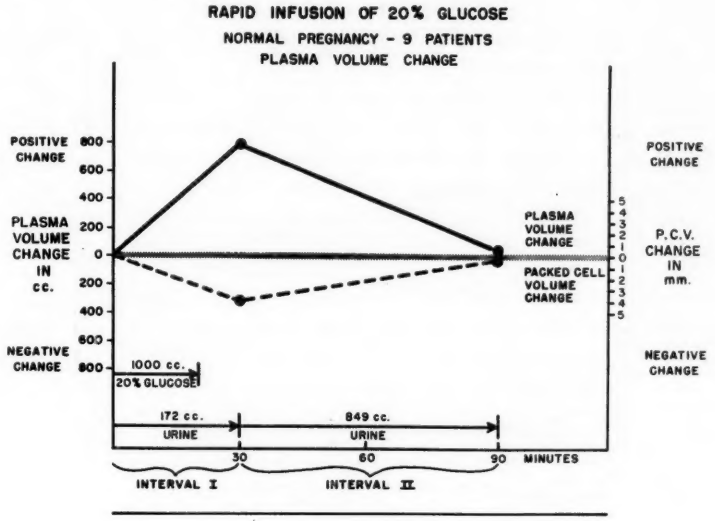

Fig. 5.

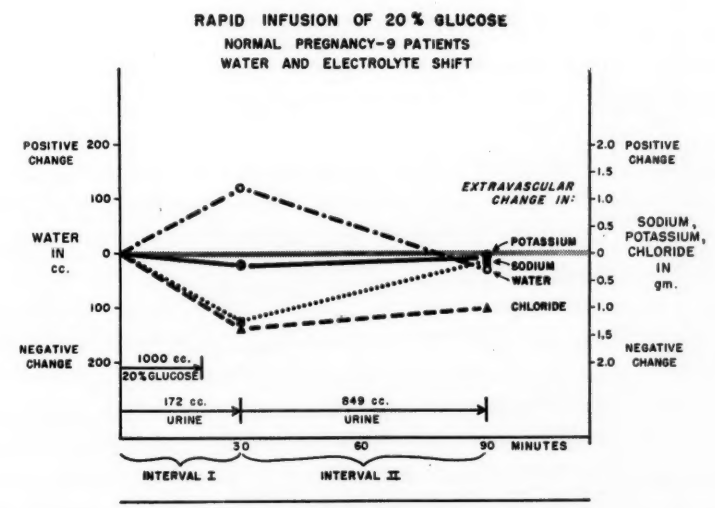

Fig. 6.

the water content of the extravascular compartment. There remained, however, a marked net gain of water by the extravascular compartment. The sodium concentration of the extravascular compartment returned to its pre-

infusion level, whereas a net loss of chloride by that compartment persisted. There was no significant change in potassium distribution during interval I or II. The total urinary output during intervals I and II was 661 c.c.

Phase II. Hypertonic Solutions of Glucose.—

Normal pregnancy: Fig. 5 illustrates the mean changes in plasma and packed-cell volumes produced in 9 normal pregnant patients. A marked increase in the plasma volume was produced during interval I. This was associated with a decrease in the packed-cell volume representing a significant degree of hemodilution. During interval II, both the plasma and packed-cell

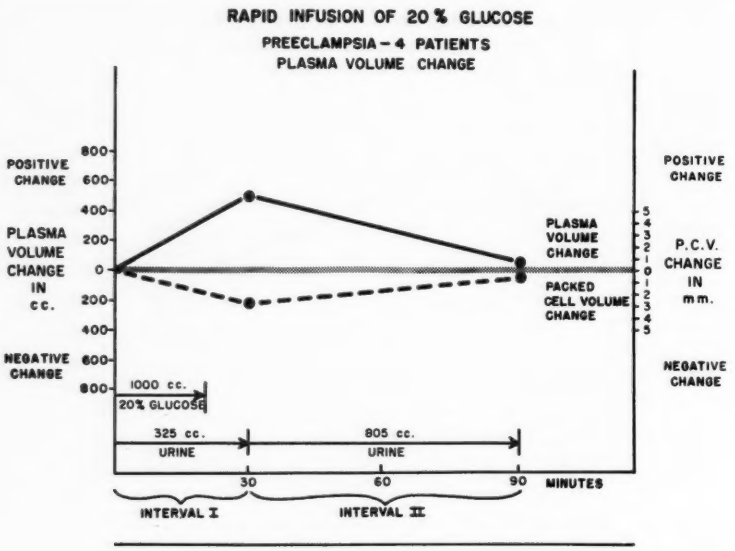

Fig. 7.

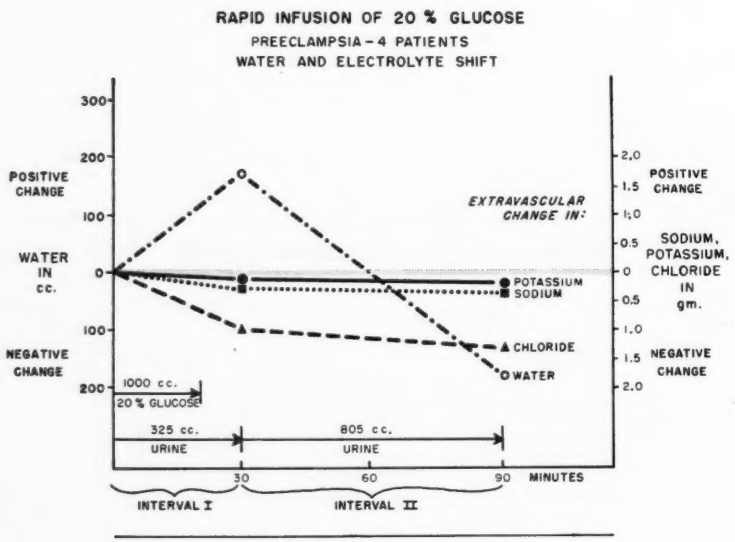

Fig. 8.

volumes returned to their preinfusion levels. Fig. 6 illustrates the changes in the distribution and shift of water and electrolytes in the extravascular compartment produced by the infusion of a 20 per cent solution of glucose into nor-

mal patients. During interval I there was a shift of approximately 120 c.c. of water from the vascular into the extravascular compartment. There was a significant shift of sodium and of chloride from the extravascular into the vascular compartment. During interval II, the shift of water, sodium, and chloride was reversed. There was a return of water and sodium to their preinfusion levels. There was, however, a net loss of chloride by the extravascular compartment. The over-all effect, then, of the infusion was the production of a net loss of chloride by the extravascular compartment. There was no significant alteration in potassium distribution. The total urinary output during intervals I and II was 1,021 c.c. No net change in body water balance was produced.

Pre-eclampsia: Fig. 7 illustrates the effect of 20 per cent glucose solutions on the plasma and packed-cell volumes of 4 pre-eclamptic patients. During interval I, there was a marked increase in the plasma volume and a corresponding decrease in the packed-cell volume. During interval II, the plasma and packed-cell volumes returned to their preinfusion levels. Fig. 8 illustrates the changes in extravascular water and electrolytes in these 4 pre-eclamptic patients. During interval I, there was a shift of approximately 175 c.c. of water from the vascular into the extravascular compartment. There was no significant change in the concentration of sodium and potassium, but there was a significant shift of chloride from the extravascular into the vascular compartment. During interval II, the most significant change observed was the marked shift of water from the extravascular into the vascular compartment. This water shift was not associated with a proportionate shift of sodium and of chloride. There resulted, then, a net loss of water by the extravascular compartment as well as a net loss of chloride. There was no significant alteration in sodium or potassium distribution. The total urinary output during intervals I and II was 1,130 c.c. This represents a slightly negative body-water balance.

Comment

The data obtained in this investigation have provided additional factual support for the contentions of Dieckmann,[4] Mengert,[7] Freis,[1] and others that the intravenous administration of solutions of 5 per cent glucose in water to patients with pre-eclampsia frequently increases the quantity of water retained by those individuals.

The administration of 5 per cent solutions of glucose in water to normal pregnant patients produced a true hemodilution. This increase in plasma volume is not so great as one usually finds in nonpregnant patients under similar conditions. The hemodilution produced in these normal pregnant patients was associated with a significant shift of sodium and of chloride from the extravascular into the vascular compartment. A plausible explanation for this is that, for the maintenance of a normal electrolyte concentration of the serum, the extravascular depots supply the needed sodium and chloride.

The infusion of 5 per cent solutions of glucose in water into patients with pre-eclampsia produced some hemodilution, but not as much as was produced by the same type of fluid when administered to normal pregnant patients. By inference, it is assumed that this quantity of water which could not be accounted for by the increase in plasma volume and the urinary output had shifted out of the vascular compartment and into the extravascular compartment. Associated with this marked shift of water out of the vascular compartment, there was

a shift of sodium and of chloride out of the extravascular compartment and into the vascular compartment. During the one-hour interval following the completion of the infusion, the plasma volume generally returned to its preinfusion level and the sodium returned to its preinfusion level. The extravascular compartment retained approximately twice as much water as did the same compartment in the patients without pre-eclampsia. It is believed that this finding provides factual support for the clinical impression that the use of 5 per cent solutions of glucose in water do not produce the desired effects when given to patients with pre-eclampsia.

The administration of 20 per cent solutions of glucose in water to normal pregnant patients produced a greater degree of hemodilution than did the 5 per cent solutions of glucose. The plasma volumes returned to their preinfusion levels within an hour after the completion of the infusions. The total urinary output for the study intervals equaled the infusion volumes, hence no change in body water balance was produced. The only lasting effect of the hypertonic glucose solution was a net loss of chloride by the extravascular compartment.

Hypertonic glucose solutions administered to patients with pre-eclampsia produced approximately one-half as much hemodilution as was observed in normal pregnant patients. The plasma volumes returned to their preinfusion levels at the end of the study interval. During the study interval, there was an average output of 1,130 c.c. The over-all effect, then, was the production of a slightly negative body-water balance. Brown and Bradbury[8] reported that the administration of hypertonic fluids to patients with pre-eclampsia produced a temporary diuresis but no net decrease of the body-water balance when measured over a twenty-four-hour period. Under the conditions of the investigation herein reported, sodium and chloride shifts did not always parallel the water shift. The comparison of the effects of 5 and of 20 per cent solutions of glucose in water on patients with pre-eclampsia permits the conclusion that, under the conditions of this investigation, both produced hemodilution although the hemodilution produced by the hypertonic glucose solution was more pronounced. The hypertonic solutions produced a urinary output equal to or slightly greater than the volume of water administered, whereas solutions of 5 per cent glucose in water produced a positive water balance. This difference can probably be explained by the greater osmotic pressure of the concentrated solution which interferes with or hinders the flow of water from the vascular into the extravascular compartment. The hypertonic solutions produced a temporary diuresis, but this diuresis was insufficient to effect the excretion of significantly greater quantities of water than were administered. Although the water in both types of solutions enters the extravascular compartment rapidly, a 5 per cent solution of glucose effects a more persistent and increased extravascular water content (water logging of tissue) than does a 20 per cent solution. For this reason, there seems to be no real justification for the employment of a 5 per cent solution of glucose in the treatment of pre-eclampsia. Neither 5 nor 20 per cent solutions of glucose significantly affect sodium retention or excretion.

These observations support the findings of Dieckmann, Mengert, Freis, and others that the administration of 5 per cent solutions of glucose to patients with pre-eclampsia produces a net gain of body water by those individuals. Hypertonic glucose solutions, on the other hand, produced a temporary diuresis but no significant change in body-water balance.

The data also support the findings of Crutchfield,[9] Peters,[10] de Alvarez,[11] and Turner[12] that water diuresis does not necessarily imply sodium diuresis as well.

The data presented fail to show any significant shift of potassium from one compartment to another either in normal patients or in patients with pre-eclampsia. This may be explained by the findings of Moore,[13] who demonstrated in nonpregnant patients that radioactive potassium required at least 15 hours to shift from the vascular into the extravascular space. Sodium, on the contrary, required one hour or less for the same redistribution. There is little evidence at the present time that potassium metabolism is seriously altered by pre-eclampsia.

In view of the fact that in this investigation no significant negative water balance could be produced by isotonic or hypertonic solutions of glucose, the rationale for parenteral-fluid therapy must be something other than the production of dehydration. In order to effect adequate urinary function with regard to water excretion without producing a greater positive water balance, solutions of 20 per cent glucose in water were used. The glucose solutions were administered rapidly in order that the hypertonicity be maintained for a suitable period of time prior to being nullified by dilution factors.

The volume of water administered during the therapeutic regime now in effect on this service is arbitrarily set at 1,500 c.c. plus the urinary volume for a twenty-four-hour interval. Five hundred cubic centimeter units of this total volume are given rapidly and spaced more or less equally over a twenty-four-hour period. Between the units of hypertonic fluid, the infusion is continued at the slowest possible rate which will maintain needle patency. This regime has been in effect for approximately six months, and is proving to be a very satisfactory approach to the problem of parenteral-fluid therapy in patients with severe pre-eclampsia.

Summary and Conclusions

1. Five per cent solutions of glucose produced *a net gain in body water* (''water logging'') when administered to pregnant patients. This gain in body water is much greater in patients with pre-eclampsia than in normal pregnant patients.

2. In contrast to this, 20 per cent solutions of glucose produced *no significant net change in body water* when administered to normal pregnant patients or to patients with pre-eclampsia.

3. The hemodilution produced in pre-eclamptic patients by means of either 5 or 20 per cent solutions of glucose is of short duration.

4. Sodium retention was not altered by the use of either 5 or 20 per cent solutions of glucose in patients with pre-eclampsia.

5. Potassium distribution was not affected by the use of either 5 or 20 per cent solutions of glucose in patients with pre-eclampsia.

6. On the basis of the results obtained in this investigation, 20 per cent solutions of glucose are recommended for the treatment of pre-eclampsia when administration of intravenous fluid is indicated.

I wish to express my gratitude to Dr. Alvin H. Lassen and Misses Marie St. Raymond and Orris Hall for their valuable assistance in the preparation of this paper.

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New Instruments, Etc.

A FATAL COMPLICATION OF GYNECOLOGICAL SURGERY*

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THE purpose of this paper is to present the recent syndrome of acute staphylococcal pseudomembranous enterocolitis following antibiotic therapy, and to add a case of our own which occurred incidentally to gynecological surgery. About twenty cases of this syndrome have been reported in the literature, not all of them following surgery.

A 21-year-old white woman, gravida 0, married nine months, was admitted to the Gynecological Service of Fordham Hospital with the chief complaint of lower abdominal pain. On the day prior to admission the patient suddenly developed severe pain in the right lower quadrant, followed by diarrhea and flatulence for which a physician gave her penicillin and Terramycin. Despite this therapy the pain persisted and became progressively more severe. The diarrhea continued, and vomiting developed on the day of admission.

Appendectomy had been performed nine years before. Nevertheless, she complained of recurrent episodes of right lower quadrant pain. A history of recurrent purulent vaginal discharge and therapy for chronic cervicitis was elicited. Terramycin, 2 Gm. daily, without medical supervision had been taken sporadically for a six-month period.

The physical examination revealed a well-developed, well-nourished woman in no acute distress. The temperature was 102½ F.; the blood pressure was 132/76. Eye, ear, nose and throat examination was completely normal. No nuchal rigidity or lymphadenopathy was found. A regular sinus rhythm was present, and there were no murmurs. The lungs were clear.

The abdomen was soft, with tenderness only on deep palpation and slight muscle guarding in the lower right quadrant without rebound tenderness. There were no palpable abdominal masses. The liver and spleen were not felt. Bimanual pelvic examination revealed normal adult external genitals and a two-finger introitus with good support. There was no discharge from the Bartholin, urethral, or Skene glands ducts. The cervix was long, conical, eroded, and without pain on motion. The uterus was smaller than normal, acutely anteflexed, and movable. The left adnexa were normal, and in the right adnexal region close to the pelvic wall a cystic tender mass about 4 cm. in diameter was felt.

With these findings the possibilities of ectopic gestation, right cystic ovary, or torsion of a right ovarian cyst were considered. During the next two days the temperature ranged from 99° to 102° F. The pain persisted. The red blood count, hemoglobin, and urinalysis were normal. The white blood count rose from 11,000 to 13,000. Chest x-rays and electrocardiogram were normal. On the third hospital day pelvic examination revealed the right adnexal mass to have doubled in size, and an exploratory laparotomy under spinal anesthesia was performed.

A hemorrhagic right ovarian cyst, 8 cm. in diameter, was found. This cyst was enucleated and the ovary preserved. All pelvic organs, as well as the liver, gall bladder,

*Presented at a meeting of the Bronx Obstetrical-Gynecological Society, Nov. 23, 1953.

stomach, and intestines, appeared normal. The immediate postoperative condition was good. The pathological report of the excised cyst read: "Fragment of ovarian tissue containing corpus luteum and follicle cyst. No evidence of malignancy."

On the first postoperative day the temperature rose to 104° F. Vomiting and severe diarrhea developed. Therapy at this time included intravenous fluids, glucose, electrolytes, and Terramycin. The abdomen was soft. The red blood count, hemoglobin, and urinalysis were normal, but the white blood count had risen to 17,500, with a shift to the left. Her condition remained the same on the following day, but on the third postoperative day the temperature rose to 105.6° F. Diarrhea and vomiting persisted. There was no abdominal pain or distention. The operative wound appeared to be healing and was free of infection. Chest examination, x-rays of the chest and abdomen, urinalysis, and blood culture were all negative. A Levin tube was inserted and suction started.

The following day the patient became semistuporous. The temperature ranged from 102° to 105° F. The vomiting persisted and the vomitus became like coffee grounds. Severe diarrhea recurred. The patient went into collapse, the blood pressure falling to 80/40. She was given intravenous Wyamine and ACTH. The white count had risen to 25,000. Blood chemistry determinations revealed the blood urea nitrogen to be 34 mg. per cent; uric acid, 4.6 mg. per cent; sugar, 195 mg. per cent; and carbon dioxide combining power, 30 volumes per cent. The blood culture again was negative, as was the smear for malarial parasites. Stool examination revealed a 4+ Benzedrine reaction.

Surgical and medical consultations offered a variety of diagnoses, including subacute bacterial endocarditis, meningoencephalitis, and severe enteritis. The Widal test, as well as stool cultures for typhoid, Shigella, and paratyphoid, was negative. Nose and throat cultures revealed hemolytic streptococci and hemolytic *Staphylococcus aureus*. All agglutination tests for enteric bacilli were negative.

The patient died on the sixth postoperative day, still exhibiting severe hyperpyrexia, vomiting, and diarrhea. Therapy had included multiple whole blood transfusions, large doses of antibiotics including penicillin 1,000,000 units every two hours, Terramycin 2 Gm. daily, sulfadiazine, Aureomycin, and Chloromycetin, all intravenously.

At autopsy, the skin incision, as well as the fascial and peritoneal suture lines were found to be well healed. The most important findings were in the gastrointestinal tract: all serosal surfaces were normal. The esophagus, stomach, and duodenum showed no significant changes other than autolysis. The jejunum had areas of congestion in the mucosa but no ulcerations or erosions. At the level of the ileojejunal junction a severe change occurred. On opening of the bowel, long, soft, reddish-gray flat, "noodlelike" segments were found free within the bowel lumen. They showed a mucosal pattern, and it was apparent that there had been a complete separation of necrotic mucosa from the submucosa. The underlying submucosa was hemorrhagic and raw. An occasional small patch of mucosa still remained. The entire large bowel exhibited different changes. The mucosa, as well as the entire wall, was thickened, and covered in its entirety by a fibrinous layer. There was no generalized ulcerative disease. Other findings at autopsy included meningeal injection, evidence of aspiration of coffee ground vomitus; and normal heart, liver, adrenals, and kidneys. The uterus was normal in size; and the right ovary was found incised and sutured. The cervix was eroded, and the endometrium appeared gelatinous.

Postmortem bacteriological studies from the uncovered ileal surface showed *Staphylococcus aureus* hemolyticus, coagulase positive of a highly virulent stain. Several media plates were negative for typhoid, paratyphoid, and Shigella.

Sections at various levels of the intestine presented a severe membranous type of necrosis with extension into the submucosa and muscularis. There were numerous polymorphonuclear leukocytes and clouds of gram-positive bacteria enmeshed in the necrotic tissue and fibrin. These were referred to by the pathologist as "microabscesses." Examination of the liver, kidneys, and brain by the Medical Examiner indicated no signs of heavy metal or other poisons.

The pathological diagnosis was: (1) pseudomembranous enterocolitis caused by a *Staphylococcus aureus* hemolyticus; (2) terminal bronchopneumonia; (3) chronic cervicitis and endocervicitis.

In summary, we have reported upon a patient admitted with abdominal pain, fever, and diarrhea, and a palpable ovarian mass, who underwent surgery because of the increasing size of the mass. She had been taking Terramycin intermittently for six months and received this and other antibiotics both pre- and postoperatively. Her postoperative course was characterized by fever, severe vomiting, and diarrhea, with collapse and death. The autopsy findings led to the diagnosis of acute pseudomembranous enterocolitis caused by hemolytic *Staphylococcus aureus.*

Terplan and associates[1] of Buffalo reported 6 postoperative deaths in patients who underwent operative procedures and who received one of the following antibiotics: Terramycin in 2; penicillin and streptomycin in 3; and penicillin, Terramycin, and Aureomycin in one case. The causative agent responsible for the acute desquamative and membranous enterocolitis terminating in a shocklike state and death was demonstrated in the exudate within the lumen, and in the floating membranes covering the surface of the acutely inflamed intestinal tract. In all cases, masses of gram-positive cocci, identified as hemolytic *Staphylococcus aureus* were found in the intestinal tract. Not only were they not affected by antibiotics which normally are lethal to this staphylococcus, but, indeed, later experiments proved that the bacteria flourished in a medium to which the antibiotic was added.

In all, the clinical course and pathological pictures were similar: nausea and vomiting followed by severe progressive watery diarrhea, occurring from the first to the fourth postoperative day, with death between the third and eighth postoperative days.

The most striking feature which led to the belated recovery of hemolytic staphylococcus in pure culture in one of the cases was the presence of exuberant masses of the organism in the shed watery exudate. There had been no septicemia. These findings support the clinical and bacteriological observations of Jackson and Finland[2] in patients treated for pneumonia with Terramycin. In four such cases of severe "superinfection," pathogenic staphylococci were recovered from their stools.

Similar complications were observed by Womack[3] in the course of Terramycin therapy of urinary tract infections. No postmortem bacteriological or gastrointestinal findings were described, but severe vomiting and diarrhea following Terramycin therapy with fatal termination was reported. However, staphylococcic dysentery and pneumonia were presumably the cause of death in one case as that organism was repeatedly cultured from the sputum and stool.

Additional information regarding staphylococcic enteritis as a complication of antibiotic therapy was reported by Dearing and Heilmann[4] from the Mayo Clinic. Severe diarrhea and shock developed in these cases following Terramycin therapy and in one case after Aureomycin. At postmortem examination pseudomembranous jejunitis, enteritis, or enterocolitis was found in all 4 cases. Included in this series are data on an 8-year-old child who was treated for simple pharyngitis with Terramycin. The major postmortem finding in this case, too, was pseudomembranous colitis.

Severe pseudomembranous colitis following Aureomycin and Chloromycetin, corroborated by postmortem findings, was reported by Reiner.[5]

Bernhart[6] from Switzerland reports 2 cases very similar to those of Jackson and Finland in which surgery was performed and Terramycin administered on the third and fifth days in both cases. Severe enterocolitis was found at postmortem. Gram-positive cocci were cultured post mortem from the feces.

The French have reported similar cases of antibiotic therapy followed by diarrhea, collapse, and death when pseudomembranous enterocolitis on a staphylococcic basis was found at postmortem.

In the case here reported from Fordham Hospital, sensitivity studies on the intestinal organisms were performed. The bacteria were resistant to penicillin, Terramycin, and Aureomycin, but sensitive to Erythromycin. This substantiates the work of Dearing and Heilmann who report that the organisms recovered not only were resistant to the therapeutic drug but actually flourished when it was added to the culture medium. Erythromycin was the only drug which inhibited the growth of the cultured organism.

Since Erythromycin is one of the newer antibiotics and has not been widely used, it is probable that, with increased administration, the syndrome of staphycoccic pseudomembranous enterocolitis will result from its usage as well.

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MALIGNANT BRENNER TUMOR

Report of a Case

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IT IS generally believed that the Brenner tumor is invariably benign. Recently Dubrauszky[1, 2] has reported two cases of malignant Brenner tumor and has found two older case reports in a review of the literature. Still more recently, Limburg[3] has identified an additional case. In view of the rarity of the malignant variant of the Brenner tumor, and the limited documentation of this controversial entity to date, the following case report is presented.

Case Report

Mrs. W. L., a 70-year-old Negro woman, was admitted to Norfolk General Hospital on March 8, 1953, with the chief complaints of pain and swelling in the left leg and pain in the left hip and left lower abdomen of six months' duration.

The menopause had occurred 25 years previously and there had been no vaginal bleeding since that time. There had, however, been poor appetite, gradual loss of 16 pounds over a period of six months, increasing dyspnea on exertion, nocturia, and constipation. The patient had been treated in the medical clinic for osteoarthritis and moderate hypertension.

Physical examination showed a temperature of 99° F., pulse 90, respirations 22, and blood pressure 170/70. She appeared to be poorly nourished and asthenic. The abdomen was tense and slightly enlarged. There was generalized tenderness more marked in both lower quadrants. There was a vague sensation of a fixed mass in the left lower quadrant. Pelvic examination showed the cervix to be firm and fixed with the rest of the uterus by what felt like parametrial invasion by neoplastic tissue. The uterus seemed to be irregularly enlarged with the suggestion of a firm mass on the left side. Proctoscopy showed the rectal mucosa to be free of lesions.

An x-ray of the chest was reported as showing minimal cardiac dilatation and/or hypertrophy. A flat plate of the abdomen showed no lesions of the pelvis and hips. Laboratory examinations revealed moderate anemia and impaired renal function. An electrocardiogram was reported as essentially within normal limits.

On March 13, 1953, under endotracheal anesthesia, a dilatation and curettage was done. Very little tissue was obtained and the uterus proved to be small. After the abdomen had been opened through a low midline incision, it was found that a somewhat movable cystic mass was present on the right side arising from the left ovary. There was tumor invasion of the left broad ligament to the lateral pelvic wall. The exploratory laparotomy was otherwise negative, there being no evidence of metastatic lesions. The pedunculated mass was lifted from the pelvis and its stalk cut across, but it was impossible to dissect out all the tumor tissue.

The immediate postoperative course was satisfactory. On the evening of the second postoperative day the patient had a chill, temperature of 102.4° F., and was disoriented. She was given penicillin and intravenous fluids, and her condition rapidly improved. Deep

x-ray therapy was started on the seventh postoperative day through four portals. Each of the four portals received a total of 2,250 r measured in air. The patient was then followed as an outpatient and had no symptoms until August, 1953, when she started bleeding per vaginam.

On her second admission on Aug. 10, 1953, the patient was lethargic, anemic, and markedly dehydrated. The vaginal walls felt very hard, nodular, and both parametrial regions were infiltrated. The hemoglobin was 6.9 Gm. She was given blood transfusions and was discharged from the hospital on Aug. 18, 1953, asymptomatic. Between August 20 and 27, she received a short course of x-ray therapy consisting of 750 r measured in air through each of two pelvic portals. Therapy was discontinued when her condition had seriously deteriorated. She was again admitted to the hospital on Aug. 27, 1953, with continued bleeding per vaginam, and died the following day.

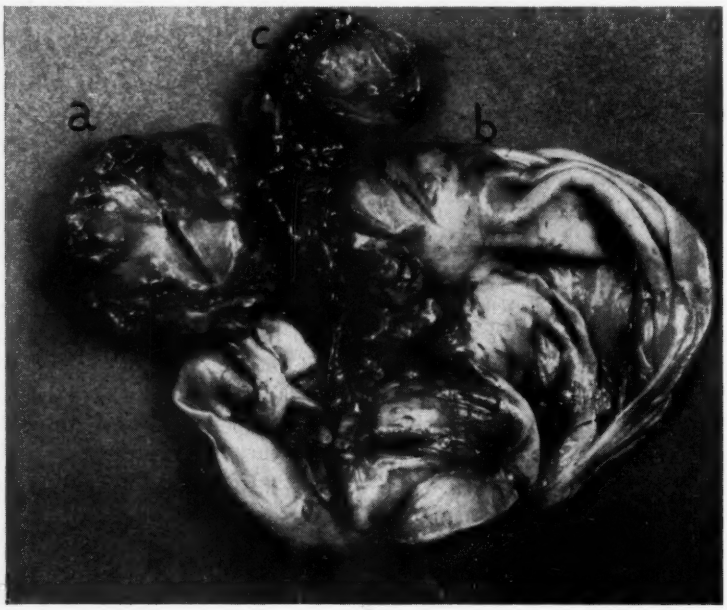

Fig. 1.—Surgical specimen. At the left is a firm encapsulated benign Brenner tumor (*a*). At the right is a partially transected fibroma (*b*) which is contiguous with the opened cyst. Between these lesions, projecting upward is a soft unencapsulated tumor (*c*) which is interpreted as a malignant Brenner tumor. The scale is the same as that shown in Fig. 5.

Pathologic examination of the surgical specimen, the left adnexa, showed it to consist of a mass (Fig. 1) which contained a unilocular cyst 8 cm. in diameter, containing clear fluid, with a thin white fibrous wall and smooth lining. The solid portion measured 5 by 3.5 by 4 cm. and was composed of two firm homogenous nodules between which there was less well-defined softer fleshy pinkish tissue. Both the firm nodules were well encapsulated. One of the nodules, 3 cm. in diameter, was attached to the cyst wall and, on section, appeared white and granular. The other nodule, 2 cm. in diameter, displayed a similar white and granular cut surface.

Microscopic section through the cyst wall and the underlying firm tumor nodule showed them to be serous cystadenoma and fibroma, respectively. Section of the other firm nodule showed a fibrous stroma within which were numerous nests of cells having an epithelial appearance and having nuclei which exhibited the "coffee bean" appearance (Fig. 2). In some of the epithelial nests there was central cyst formation and in others there were calcium deposits. This was considered to be a benign Brenner tumor. Sections taken from the unencapsulated soft portion of the specimen showed a fibrous stroma in which there were cell nests which showed some degree of resemblance to those in the

Brenner tumor (Fig. 3). The "coffee bean" appearance was not present, however, and there was a tendency toward nuclear irregularity and hyperchromatism. Occasional mitotic figures were seen. In other areas of this tissue the tumor cells were disposed in narrow columns or cords often with a central lumen (Fig. 4). The stroma appeared to be undergoing invasion by the epithelial elements described. There was no invasion of the tube by the ovarian tumor. It was believed that the invasive lesion was a malignant Brenner tumor.

Fig. 2.

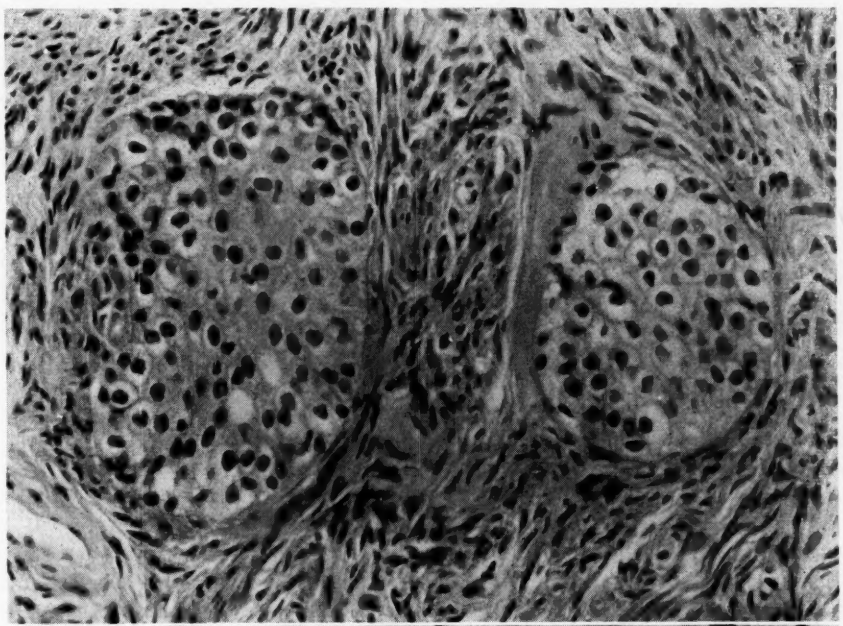

Fig. 3.

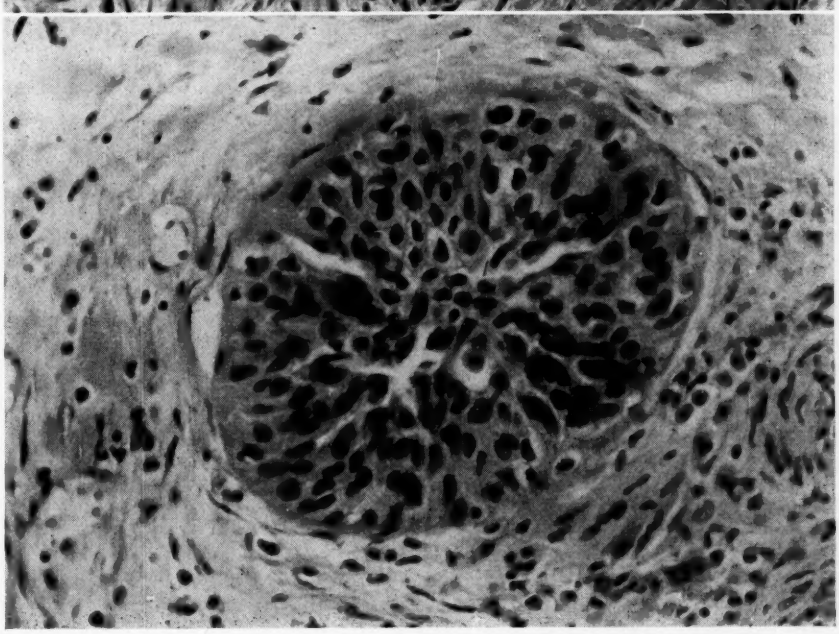

Fig. 2.—Benign Brenner tumor. Compare with Fig. 3. (×420; reduced ⅓.)
Fig. 3.—Malignant Brenner tumor. Compare with Fig. 2. (×420; reduced ⅓.)

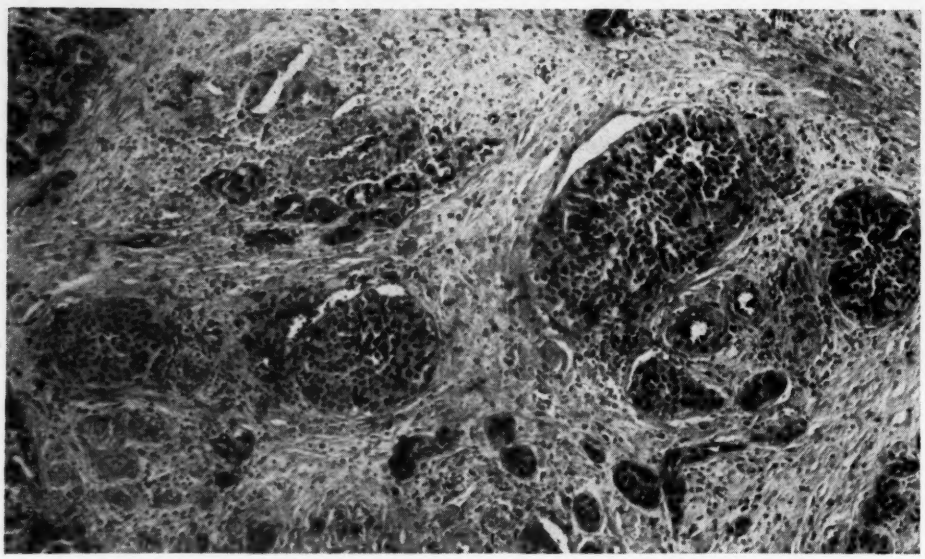

Fig. 4.—Malignant Brenner tumor. Note smaller epithelial islands with central lumen. (×100; reduced ¼.)

Autopsy.—The pertinent findings were limited to the pelvis and lower abdomen. *Genitals:* The left tube and ovary had been previously removed. The remainder of the internal genitals with the exception of the right tube formed a pelvic mass, 9 by 9 by 8 cm. (Fig. 5), which was firmly adherent to the pelvic wall particularly on the left side. It involved the posterior wall of the bladder and extended laterally to invade and obstruct the left ureter and to compress the right ureter. Posteriorly, the mass filled the cul-de-sac and invaded the muscularis of the rectum. The lower half of the uterus and the entire cervix appeared to be diffusely invaded by tumor tissue and the upper part of the vaginal wall

Fig. 5.—Autopsy specimen of pelvic viscera. Note the large cysts in the right ovary (on left-hand side of illustration), and the diffuse invasion of ovary, uterus, cervix, and vagina by tumor. The vagina lies on the right hand side of the illustration.

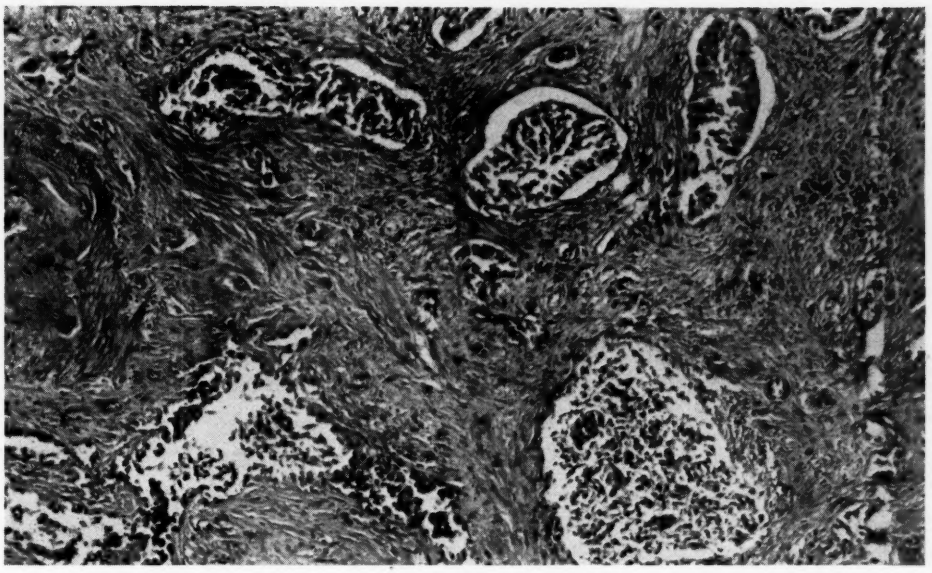

Fig. 6.—Renal lymphatics permeated by malignant Brenner tumor. (×82; reduced ¼.)

likewise appeared to be invaded by the neoplasm. In the right ovary there was a thin-walled cyst that measured 5 by 6 by 7 cm. which contained some bloody fluid. *Kidneys:* There were hydronephrosis and hydroureter bilaterally. Within the cortex of the left kidney were three indurated white areas varying from 10 to 25 mm. in diameter. *Microscopic:* Sections from various areas of the pelvic tumor mass showed an appearance identical with that of the malignant lesion already described in the surgical specimen. The tumor invaded the right ovary, uterus, cervix, vagina, bladder, and rectum. There was no invasion of the tube. Sections of the left kidney showed tumor lying within lymphatic channels (Fig. 6) and also circumscribed areas of tumor invading the kidney substance.

Comment

The clinical course of this tumor indicates only a moderate degree of malignancy. With the exception of lymphatic spread to the left kidney, the entire extension appears to have been by local invasion of the contiguous structures. It appears that in less extensive lesions good results might be expected after radical surgical extirpation.

The results of radiotherapy in this one instance suggest a high degree of radioresistance. Despite a total dosage of 1,050 r measured in air, the tumor progressed in size during radiotherapy, and comparison of the autopsy with the surgical specimen showed no histologic evidence of alteration within the tumor.

The bilateral distribution of the tumor is of some interest. Although benign Brenner tumors are occasionally bilateral, and a bilateral origin of the malignant lesion here presented must be considered, it is our impression that the tumor arose in the left ovary and involved the right by invasion or metastasis. This belief is based upon the apparent lack of involvement of the right adnexal region at the time of laparotomy.

Summary

A case of malignant Brenner tumor is presented. The tumor at the time of death had diffusely invaded most of the pelvic viscera, and had metastasized to a kidney by way of the lymphatics. A marked degree of radioresistance was exhibited. A benign Brenner tumor was present adjacent to the malignant one, but distinct from it.

Gratitude is expressed to Dr. Emil Novak for his aid in the study of this tumor.

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ABDOMINAL PREGNANCY WITH SURVIVAL OF MOTHER AND NORMAL CHILD

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ALTHOUGH abdominal pregnancies are not very uncommon, those reaching viability with survival of the mother and a normal infant are rare. For this reason this case is being reported to add to the available literature on this subject.

This is the case of J. J., a 28-year-old white para iii. Her past obstetrical history was poor. In 1945, she was delivered of a full-term, 3,150 gram male infant by breech delivery after two days of poor labor. In 1946, she delivered a male infant at 34 weeks following premature rupture of the membranes. This infant died after twelve hours. In 1947, she delivered another male infant at 34 weeks after premature rupture of the membranes. This infant weighed 2,130 grams and survived.

Her past medical history was negative. She had been married eight years; catamenia was at 13 with periods every 28 days, flowing 5 days, with no dysmenorrhea. Her past surgical history was as follows. In 1941 she had a Baldy-Webster type uterine suspension at which time the right tube and appendix were removed and the cervix was conized. In 1949 she had a cholecystectomy.

With her present pregnancy and illness, she was first seen March 28, 1952, because of pain in the lower abdomen and scant vaginal bleeding of two days' duration. Her last menstrual period was Feb. 5, 1952. Pelvic examination revealed the uterus somewhat softened and enlarged. The left adnexa were tender but no mass was felt. She was admitted to Corwin Hospital for observation with the diagnosis of ectopic pregnancy or threatened abortion. Urinalysis was negative. The red cell count was 4.65 million, hemoglobin 11.9 Gm., white cell count 8,550 with a normal differential. The next day all pain had subsided with no more bleeding and the patient was discharged.

She reported regularly for prenatal care and her course was uneventful. She complained, however, of excessive and painful fetal movements. The placental souffle was low and the baby was in the transverse position at 32 weeks. A placenta previa was suspected.

She was again admitted to the hospital Sept. 21, 1952, being approximately 34 weeks pregnant, with pain in the right side of the abdomen and lumbar region. Urinalysis was negative and the hemoglobin was 12.4 Gm. The next day she felt much better. An x-ray was taken in an attempt to localize the placenta. This showed the baby in a vertex posipostion, left occipitoanterior at about 34 weeks' gestation. Placenta previa could not be excluded but the radiologist reported that the shadow in the pelvis could include the placenta. A shadow in the left lower quadrant of the abdomen, which was the uterus, was overlooked at this time.

The next morning, Sept. 23, 1952, the pain suddenly became more severe, and the abdomen was very tender and rigid. Her blood pressure was 80/60 and she had air hunger. The fetal heart tones were good. The red cell count was 2 million, hemoglobin 6.2 Gm., white cell count 12,600 with a shift to the left. There had been no external bleeding. Blood transfusion was started immediately and the patient was prepared for surgery with the preoperative diagnosis of partial separation of the placenta with concealed hemorrhage.

On opening the abdomen there was about 800 c.c. of free clotted and unclotted blood. A large bluish sac containing the fetus filled the abdomen. There was a rent in the right lateral surface from which there was free bleeding. The sac, which appeared relatively avascular, was incised anteriorly, and the baby was extracted, breathing and crying spontaneously. Bleeding was excessive and the bleeding areas along the incision were controlled with hot packs while more blood was started in the other arm under pressure.

The uterus, which was about the size of a 2½ to 3 months' pregnancy, was embedded in the left lower quadrant of the mass. The placenta was attached to the sigmoid colon, posterior and superior surfaces of the uterus, cecum, small bowel, and posterior peritoneal surfaces over the large vessels. A large portion of the placenta was membranaceous in type. The free placenta and membranes were trimmed, and the vessels ligated, but the greater part of the placenta was left in situ. Because of the large amount of placenta attached to the serosal surface of the uterus and because the patient had no wish for future childbearing, no attempt at conservative treatment was made and a supracervical hysterectomy was performed. The abdomen was closed in layers without drainage.

The patient received 2,500 c.c. of whole blood and was returned to her room in good condition. She was placed on 400,000 units of procaine penicillin every 8 hours and her convalescence was uneventful except for a temperature of 102° F. on the second and third postoperative days. She was discharged on her tenth postoperative day in good condition. On examination at 6 weeks post partum no masses or evidence of the remaining placenta could be found. The patient has remained in good health since that time. The patient's breasts did not fill post partum, showing the role of the removal of the placenta in initiating lactation.

The female infant weighed 2,220 grams at birth and appeared perfectly normal on physical examination by a pediatrician. She remained in the hospital 25 days and was discharged in good condition on Oct. 18, 1952, weighing 2,400 grams. Her course since then has been normal and at the present time she is a normal child mentally and physically for her age.

The pathological report showed that the uterus measured 10 by 9.5 by 7 cm. with an endometrium measuring 1 to 1.2 cm. in thickness. There were several small intramural myomas. Grossly no portion of the left Fallopian tube could be identified. Microscopically the endometrium showed a marked decidual reaction. In one portion of the placenta removed, part of the fimbriated end of the Fallopian tube was identified.

Comment

Several very comprehensive reviews have been published on abdominal pregnancy.[1, 2, 3] From these surveys, Suter and Wichser[3] have estimated that: "Only about one-fourth of all the extrauterine pregnancies diagnosed after the fifth month of gestation will result in viable, living babies. About one-third of all these living, viable babies delivered from extrauterine pregnancies will have major or minor deformities including those which were incompatible with life. Approximately half of all the viable, living babies delivered from extrauterine pregnancies will survive eight days or more."

Cross, Lester, and McCain[4] and Jarcho[5] have very admirably covered diagnosis and treatment of ectopic pregnancies including advanced abdominal pregnancies. Although there is disagreement as to the removal of the placenta, it is fairly well established that, with a viable fetus, attempted removal of the placenta may result in disastrous hemorrhage. It is felt that complete removal of the placenta in this case would have been fatal.

There were sufficient diagnostic points present in this case for a correct diagnosis to have been made preoperatively if the condition had been borne

in mind, namely: (1) Symptoms suggestive of a tubal abortion early in the pregnancy. This was a clear-cut case of a secondary abdominal pregnancy resulting from a tubal abortion. (2) Transverse lie of the fetus during most of the pregnancy although the baby was in vertex position at the termination. (3) Complaints of excessive and painful fetal movements. (4) Displacement of the cervix anteriorly and upward with no effacement. (5) Flaccidity of the abdominal wall, although in this case this was attributed to an atonic abdominal wall and uterus due to multiparity. In retrospect, however, no uterine contractions were ever felt. (6) The uterus in the left lower quadrant of the abdomen, seen on x-ray and palpated but confused with the fetal head, should have been recognized.

Even though the diagnosis was not made preoperatively, we feel very fortunate in the outcome of the mother and baby. I believe the factor largely responsible for the favorable outcome in this case was the availability of whole blood and antibiotics.

Summary

1. A case of abdominal pregnancy at 34 weeks with survival of the mother and a normal child has been reported.

2. The placenta was left largely in situ which is probably the procedure of choice with a viable baby and active placenta.

3. Availability of whole blood and antibiotics is probably the reason for more survivals, especially in the mother, reported in recent years.

4. More cases should be recognized preoperatively if this condition is considered with an abnormal pregnancy.

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LEUKEMIA IN PREGNANCY TREATED WITH URETHANE

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THE occurrence of leukemia in pregnancy is relatively rare. The discovery of this complication of pregnancy has been reported in 115 instances. It is the purpose of this paper to report the use of a specific therapeutic agent, Urethane, in a case of chronic myelogenous leukemia complicating pregnancy.

Mrs. E. B., 22-year-old primigravid white housewife, was referred to the Reading Hospital on June 12, 1952, complaining of fatigue. She had been well until two months prior to admission when she developed headaches, nausea, indigestion, anorexia, and generalized weakness. Dizziness, exertional dyspnea, bleeding gums, and ankle edema were also present. The last normal menstrual period had occurred on March 17, 1952.

Physical examination revealed the temperature to be 98.6° F., pulse 85, respirations 20, blood pressure 120/68. There was moderate pallor of the skin and mucous membranes of the oral cavity. Three small petechiae of the buccal mucous membrane were noted. The liver was enlarged 4 cm. below the right costal margin. It was smooth and firm. The spleen was posterior, soft, and enlarged almost to the level of the umbilicus. The heart and lungs were normal.

Pelvic examination showed that the uterus was retrocessed and symmetrically enlarged to the size of an eight to ten weeks' gestation. The left ovary was slightly enlarged and prolapsed into the cul-de-sac.

Laboratory studies showed that the Rh factor was positive to CD and negative to E antigens. The Wassermann test was negative. Hemoglobin was 8 Gm.; erythrocytes, 3.13 million; color index, 0.8; leukocytes, 124,000; filamented neutrophils, 34 per cent; nonfilamented neutrophils, 22 per cent; eosinophils, 2 per cent; basophils, 7 per cent; lymphocytes, 3 per cent; myelocytes, 4 per cent; myeloblasts, 3 per cent; promyelocytes, 9 per cent and metamyelocytes, 16 per cent. Red-cell study showed basophilic stippling with occasional polychromasia. Bleeding time was one minute, fifty seconds. The Lee-White coagulation time was five minutes, fifteen seconds. Sternal bone marrow smear showed overwhelming numbers of promyelocytes, myelocytes, and segmented polymorphonuclear leukocytes. Erythrocytic progenitors were few in number, but numerous platelets were seen. The van den Bergh reaction was within normal range.

Because the patient was depressed and the family was anxious to have her at home, she was discharged on March 21, 1952, without specific treatment. The discharge diagnosis was chronic myelogenous leukemia with intrauterine gestation.

When readmitted on July 7, 1952, in addition to the previously noted complaints, the patient had pain in the left side of the chest. Physical examination showed no change in weight or other findings. The blood count at this time showed hemoglobin 7.5 Gm.; leukocytes 125,000; platelets 80,000. The blood smear showed 10 per cent basophils and 37 per cent early leukocytic forms. Definitive therapy was instituted in the form of corticotropin, 20 international units every six hours for five days until the platelet count increased. Urethane was then started at a level of 0.6 Gm. every eight hours for three days, after which 1 Gm. was administered every eight hours for seven days until discharge on July 24, 1952.

The patient was followed carefully on Urethane therapy. By Sept. 17, 1952, the hemoglobin was 10.5 Gm. and the leukocyte count was 10,900 per cubic millimeter with

no immature forms. The platelet count at that time was 277,000. The spleen had receded to the costal margin. There was no evidence of bleeding from the gums. The patient was tolerating her pregnancy well. She was cheerful and cooperative. Her strength had returned remarkably well. The blood pressure during pregnancy ranged from 110/50 at the fifth month to 120/80 at term. The weight rose from 119½ to 136¼ pounds. The fundus at term measured 27 cm. from the symphysis. Fetal heart tones were first heard during July, 1952, and remained consistently normal between 148 and 160 per minute.

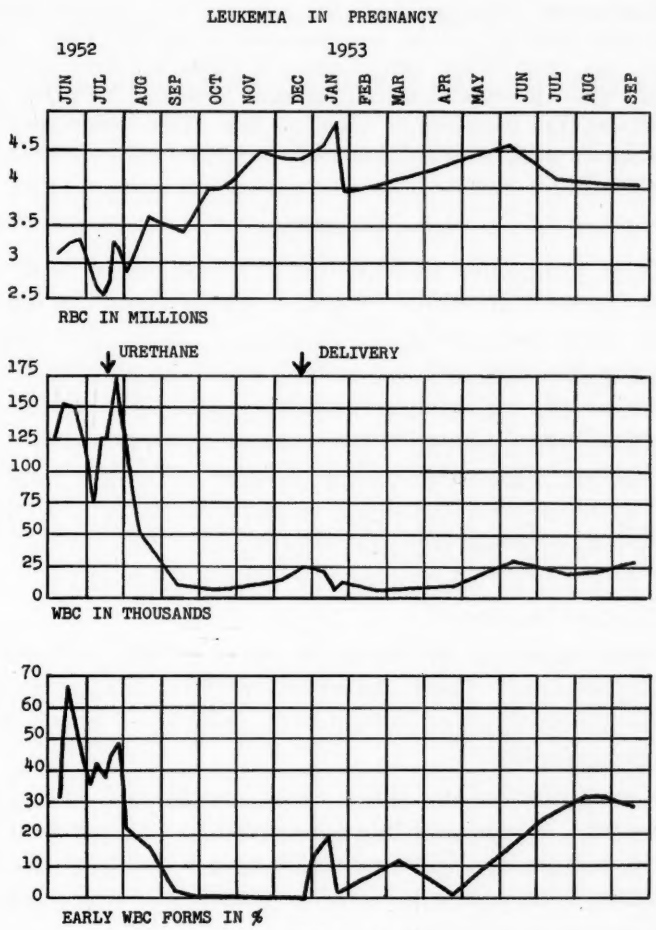

Fig. 1.

The patient was readmitted to the hospital on Dec. 29, 1952, in active labor. A twelve-hour labor was adequately controlled by two doses of Demerol, 50 mg., and one dose of scopolamine, 0.4 mg. The patient was delivered of a living male infant by elective outlet forceps with Tucker-McLane blades. A midline episiotomy was repaired in the usual fashion. Anesthesia consisted of a perineal block of 1 per cent procaine and nitrous oxide-oxygen anesthesia. Blood loss was estimated at less than 50 c.c. The infant cried spontaneously.

The patient's postpartum course was uneventful. On the first postpartum day, the hemoglobin was 11 Gm.; erythrocytes 4.45 million; leukocytes 17,000; platelets 200,250. The differential count showed filamented neutrophils 82 per cent; nonfilamented neutrophils 11 per cent; eosinophils 1 per cent; basophils 3 per cent; and lymphocytes 3 per cent. No blast cells were found. The baby showed no evidence of leukemia.

The patient developed some bright bleeding and cramps on Jan. 22, 1953. There were marked weakness and fatigue. The cervix was found to be open and bleeding was moderately severe. The uterus, well in third-degree retroversion, measured 3½ inches in depth. It was soft and boggy. The clinical impression was subinvolution of the placental site. Fifteen-minute hot douches were prescribed daily and Methergine was administered every four hours for six doses. The response was rapid and the bleeding subsided.

Concomitant with the bleeding in January, the hemoglobin fell to 10.5 Gm., leukocytes rose to 19,600 with 2 per cent myelocytes. Slight anisocytosis and poikilocytosis were noted in the smear. The platelet count was normal. At this time the Urethane which had been maintained at 0.3 Gm. was increased to 0.6 Gm. daily. This therapy was maintained until July, 1953, when early leukocyte forms appeared in the smear of the peripheral blood. The leukocyte count at the same time rose to 26,000 per cubic millimeter. Urethane was then increased to 1 Gm. per day. This dosage has been maintained. The patient has been feeling well and has shown no bleeding diathesis. The weight has remained at her normal 114 pounds.

Comment

The rarity of pregnancy in leukemia is presumed to be due to leukemic infiltrations of the genital tract.[5] Whether the leukemia is enhanced by the pregnancy has been controversial. Angellucci[1] maintains that abortion is indicated whereas Moloney and associates,[8] and Wintrobe[11] believe pregnancy has no influence on the leukemia. The latter assert that surgical intervention may precipitate an acute phase or uncontrollable hemorrhage.

A review of the literature reveals certain statistical data. About two-thirds of the patients reported suffer from chronic rather than acute leukemia.[7] In the majority the leukemia was myeloid, two-thirds of all the cases being chronic myelocytic. A few of the women with chronic leukemia had been pregnant more than once.[11]

The maternal mortality in the acute phase is 100 per cent while in the chronic it is 36 per cent.[7] Acute exacerbation of the leukemic process may be noted following parturition and even during gestation. Severe hemorrhage is not a common complication.[10]

The fetal mortality in the acute cases was 60 per cent, in the chronic cases 16.4 per cent.[7] Premature labor occurred in 42.8 per cent of the cases.[7] No leukemia in infants has been reported as a hereditary disease, although leukemia is known in newborn infants.[7, 9] Burchenal[3] was unable to transmit leukemia from mouse to offspring.

Management of the leukemia in pregnancy has largely been supportive in nature. The deleterious effects of irradiation on the fetus have been adequately established.[6] Creskoff and co-workers[4] have successfully controlled the leukemoid state in one reported case by the use of Urethane. Since the enlarged liver and spleen are in part responsible for the high rate of premature labor, it seemed imperative to use the drug on this patient if the bleeding tendency could be immediately controlled. Thus, after corticotropin therapy had improved the bleeding diathesis, Urethane therapy was instituted. Response to therapy was judged satisfactory by regression in size of the liver and spleen, and subsequent changes in the leukocyte and platelet count. It is our opinion that while the patient morphologically was suffering

from chronic myelogenous leukemia she was seen with symptoms suggestive of the onset of an acute exacerbation. Since acute exacerbations following and during parturition have been reported,[2] the therapeutic effectiveness of Urethane may be surmised from the satisfactory blood studies and clinical status of the patient in the nine months since delivery.

Summary

1. A case of leukemia complicating pregnancy and treated by Urethane is reported.

2. Some commonly held opinions concerning this complication of pregnancy are enumerated.

3. The salvage of both a live mother and live infant using a specific therapeutic agent during pregnancy suggests that further studies along these lines should be pursued.

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CAN THE IMPLANTING TROPHOBLASTS OF THE FERTILIZED OVUM DEVELOP IMMEDIATELY INTO CHORIONEPITHELIOMA?

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HERETOFORE, all cases of nonteratomatous chorionepithelioma reported have been the sequel of the expulsion of the product of conception be this hydatidiform mole, abortus, premature or full-term fetus. So far, no case has been published where the product of conception was *ab initio* one of chorionepithelioma.

If it is possible for the product of conception to be a hydatidiform mole which may be benign or malignant, it should not be impossible for the implanting trophoblasts or chorionic cells to develop immediately into chorionepithelioma without the formation of an embryo or fetus. This, I believe, is what happened in the following case.

Case Report

C. P., 23-year-old gravida i, para i, was admitted to the Philippine General Hospital on Feb. 10, 1953, for the complaints of weakness, chest oppression, and enlargement of the lower abdomen.

Menarche was at the age of 16; menstrual periods were 3 to 4 days' duration and recurred monthly. She was married at the age of 18 to a man 19 years of age who was free of venereal disease. Her first pregnancy ended in August, 1949, in the spontaneous delivery at home of a premature 8-month fetus which lived for only one hour. She menstruated monthly thereafter. Her last menstruation was in September, 1952. She noticed that with the cessation of menstruation, the lower abdomen became enlarged, and that at the same time she had anorexia and began to lose weight.

In January, 1953, because of her growing weakness, she sought admission to a provincial hospital where a laparotomy was performed. She was told that her appendix was removed. She experienced no relief of her symptoms; so on Feb. 10, 1953, she applied for treatment at the Philippine General Hospital.

On admission, she was found to be weak, pale, and emaciated. She complained of chest oppression. Her temperature was 37° C.; pulse, 120; respirations, 24; blood pressure, 120/50 Hg. The lower abdomen showed a bulging mass, the upper border of which was 4 cm. below the umbilicus. The laparotomy wound was imperfectly healed and at two different points, it was oozing a serosanguineous discharge. Vaginal examination showed the cervix to be small and closed. There was no vaginal bleeding. The preoperative diagnosis of the admitting physician was intestinal tuberculosis; the tumor in the lower abdomen was interpreted to be a matting of intestines. So a request was made for an x-ray examination of the lungs for tuberculosis. The x-ray report was not received until after the operation.

I saw her for the first time on the operating table on February 13, and was told of the working diagnosis of intestinal tuberculosis. I noticed the two oozing points on the abdominal scar and observed that the enlargement in the lower abdomen had the contour of an enlarged uterus corresponding to that of a 3½ month pregnancy.

On laparotomy, it was found that the fundus of the enlarged uterus was much thickened and converted into a strandlike necrotic growth, loosely adherent to the ab-

dominal scar at the oozing points. The right tube was swollen, distended, and filled with a solid necrotic tumor similar to that found at the fundus uteri. The right ovary was cystic and hemorrhagic. It was the size of a goose egg and was adherent to the surrounding structures. The left ovary was also cystic, but was normal in size. The left tube was slightly enlarged. No tubercles were seen.

Total hysterectomy and bilateral salpingo-oophorectomy after the separation of adhesions were done.

Saggittal section of the enlarged uterus showed that the whole myometrium of the fundus was eaten up and replaced by a large necrotizing solid tumor which had grown beyond the serous covering. The endometrium was thickened to 3 mm. and was intact throughout its whole extent.

The right thickened tube on section showed the same kind of necrotizing tumor as found in the uterus. The right ovary was cystic and also showed the same kind of tumor (Fig. 1).

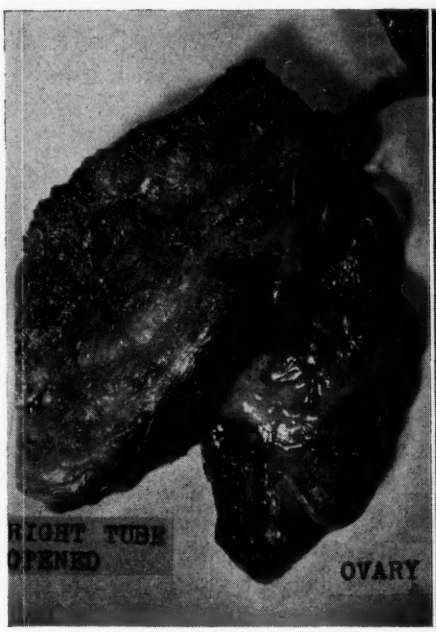

Fig. 1.

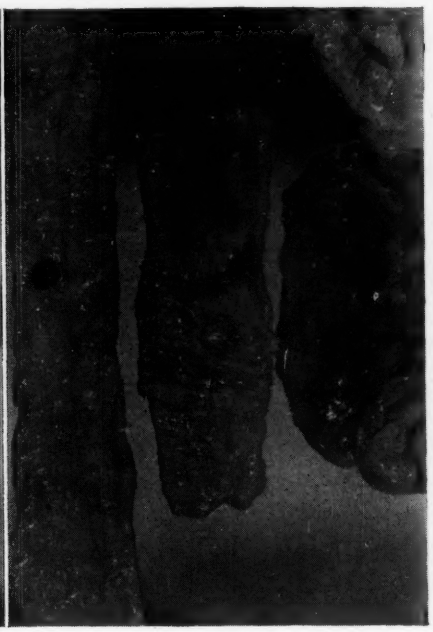

Fig. 2.

Fig. 1.—Sectioned right tube and ovary.
Fig. 2.—Metastatic chorionepithelioma in the mucosa of the duodenum, jejunum, and ileum.

Microscopically, the tumor was chorionepithelioma with a predominance of Langhans cells. The microscopic diagnosis was confirmed by Dr. Novak.

Because of the gross appearance of the tumor in the uterus, right tube, and right ovary, a frog test of the urine was performed immediately after the operation. The result was positive. The report of the x-ray of the lungs made on the day of admission gave the finding of suspicious shadows of metastasis.

Postoperative Course.—For the first three days, the patient ran a temperature between 37.5° C. and 38.8° C. and had a pulse rate of 120 or more, but on the fifth day, the temperature became normal. She ultimately recovered from the operation, gained in flesh, and walked about. The laparotomy incision healed by first intention.

The lungs which showed suspicious shadows of metastasis on admission on February 10, showed definite metastasis on February 28. They were treated daily by deep x-ray beginning on March 2, 1953, the earliest date the radiologist could be persuaded to treat the case.

On April 6, 1953, the patient noticed that whenever she coughed, the sputum was blood tinged. X-ray of the lungs at this time showed no diminution in the shadows of metastasis. She gradually grew weaker with persistence of hemoptysis.

On April 21, she complained of severe headache. An x-ray picture of the brain showed no evidence of metastasis.

On April 24, an x-ray picture of the lungs showed increase in the size and number of the metastatic shadows despite the treatment.

On May 16, a nontender mass one inch long was palpable beneath the upper abdominal incision.

On May 18, she became weak so that she remained in bed all the time. She also lost her appetite. On May 19, she had chills. Her weakness became progressive and she finally died on June 1, 1953, three months and seventeen days after hysterectomy and eight months and a few days after her last menstruation.

At autopsy multiple metastatic chorionepitheliomas were observed in the following locations:

1. Both lungs with apical and basal adhesions.
2. The mucosa of the stomach, duodenum, jejunum, and ileum.
3. Right kidney.
4. Liver, multiple, 2 cm. in diameter, lower portion of the right lobe.
5. Urinary bladder—superior wall, right side subperitoneal.
6. Anterior parietal peritoneum near the level of the umbilicus.

Comment

This case presents certain questions that call for further elucidation.

1. Can the implanting trophoblasts immediately develop into chorionepithelioma?

2. Why it is that the malignant growth in the uterus did not give rise to uterine bleeding despite its advanced development?

3. By what route did the metastases in the different organs take place?

4. Since in this case of uterine chorionepithelioma amenorrhea was associated with the corresponding enlargement of the uterus, how could such a case be differentiated from normal pregnancy in the early months before the growth went beyond the serosa of the uterus and before metastasis occurred into other organs?

1. This question poses itself because heretofore all the cases of nonteratomatous chorionepitheliomas observed or reported were preceded by the expulsion of the product of conception, or began in conjunction with hydatidiform mole as happened in 4 cases reported by me.[1] In one case of twin pregnancy I[2] reported there was the coexistence of a normal living fetus with its normal placenta (one twin) and hydatidiform (second twin) and metastatic chorionepitheliomas in the vagina and brain.

If the hydatidiform mole—abnormality of the chorionic villi—can develop without the formation of the fetus, why cannot the epithelial elements of the chorionic villi be malignant from the beginning of their existence? If the growth of the implanting cells had been in the endometrium, early bleeding would have taken place. One wonders now, how many cases that have been curetted as cases of early abortion where no fetus had existed were cases of early malignancy of the chorionic cells. Only biopsy of the curetted tissue would of course establish the diagnosis.

2. The explanation for the absence of the uterine bleeding may be found in the fact that the ovum implanted itself in the myometrium of the fundus far away from the endometrium and grew outward as solid necrotizing cords toward the abdominal cavity, leaving the endometrium intact.

3. The growth must have been very malignant judging by the widespread metastases. The metastasis in the lungs must have taken place through the circulatory route. The same perhaps may be said with regard to the growths in the liver and right kidney. The growths were found scattered in the substance of these organs. The growths, however, beneath the serous covering of the bladder and in the parietal peritoneum must have been due to direct implantation from the malignant cells that escaped from the myometrial growth into the peritoneal cavity.

The chorionepithelioma cells found in the gastrointestinal tract of this patient were attached to the mucosa of the stomach, duodenum, jejunum, and ileum (Fig. 2) unlike the intestinal growths found in the case of abdominal chorionepithelioma[3] secondary to advanced myometrial chorionepithelioma which had burst through the serosa of the uterus and had involved all the abdominal organs. In the latter case, the intestinal metastases were found just beneath the serous coat suggesting their direct implantation therein from the abounding chorionic growths in the abdominal cavity.

In the present case as well as in two other cases in our record of metastasis into the intestinal mucosa, there was an antecedent advanced pulmonary chorionepithelioma together with prolonged and persistent hemoptysis. It is most likely that the malignant cells in the intestinal mucosa of these cases were due to direct implantation of the chorionepithelioma cells which may have been swallowed from the coughed up bloody material from the lungs.

4. Myometrial chorionepithelioma immediately resulting from the fertilized ovum, not giving rise to uterine bleeding, and still confined in the uterus without metastases, would be difficult to differentiate from normal pregnancy in the early months. In both conditions, there is amenorrhea with corresponding enlargement of the uterus. In both conditions there is anorexia, weakness, and perhaps loss of weight, though the run-down condition and ill look of the patient are greater in the case of chorionepithelioma.

One may say that there is increased chorionic gonadotropin in the case of chorionepithelioma. But one must remember that in normal pregnancy, according to Eastman,[4] between the fiftieth and sixty-fifth day after the last menstruation there is an increased titer of chorionic gonadotropin from 120,000 to 500,000 I.U. per liter. After the sixty-seventh day, in normal pregnancy there is a sharp decline to 40,000 R.U. per liter, and after the one-hundred twentieth day, the value is between 1,000 and 10,000 R.U. per liter.

So it is only after the sixty-seventh or one-hundred twentieth day that quantitative determination of the chorionic gonadotropin can be used in differential diagnosis. Careful examination of the patient and the detection of metastases in other parts of the body may establish the diagnosis. In uterine chorionepithelioma, the enlargement of the uterus is perhaps not as fast nor is

its consistency as soft as in normal pregnancy because of the absence of the amniotic fluid and of the fetus. In hydatidiform mole, the uterus is often larger than it should be from the length of amenorrhea because of the cystic condition of the chorionic villi.

Conclusions

1. For the first time, a case is presented which shows that the implanting trophoblasts may be malignant *ab initio* and immediately develop into chorionepithelioma without the formation of the embryo.

2. When the implanting trophoblasts *ab initio* are malignant and take root in the myometrium of the fundus and grow outward toward the serosa without involving the endometrium, it is difficult to differentiate the malignant condition from normal pregnancy in the early months before the growth goes beyond the confines of the uterus, and before the occurrence of metastases in other parts of the body. The value of the quantitative chorionic gonadotropin test has been discussed.

3. In the early months of pregnancy when the patient complains of much low abdominal pain, of being weak, ill, and pale, one should bear in mind the possibility of myometrial chorionepithelioma. X-ray examination of the lungs for possible metastasis should be made.

Many thanks are due Dr. M. D. Cruz who furnished the accompanying illustrations.

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PRIMARY OVARIAN PREGNANCY

A Case Report

THOMAS M. WILSON, M.D., WASHINGTON, D. C.

(From the George Washington University Hospital)

NEARLY one hundred cases of primary ovarian pregnancy have been reported in the literature; of this number approximately 60 are authentic.[1] Curtis[1] states that Leopold's[2] belief that primary ovarian pregnancy results solely from fertilization of the ovum before its escape from the Graafian follicle is no longer tenable. Primary ovarian pregnancy may occur after fertilization in the oviduct, just as normal intrauterine gestation develops after fertilization in the tube.

Novak,[3] quoting Viet and Meyer, states that implantation is not necessarily within the follicle from which the ovum was discharged, especially now that we know that the secretion of the corpus luteum is necessary for implantation. The most common mechanism is probably through cortical implantation of the egg, the cortex being a favorable site because of the differentiating metaplastic potency of the germinal epithelium of the ovary.

Spiegelberg[4] listed certain criteria which are still accepted as prerequisites for a diagnosis of primary ovarian pregnancy: (1) the tube on the affected side must be intact and separate from ovary; (2) the gestation sac must occupy the position of the ovary; (3) the sac must be connected with the uterus by the ovarian ligament; and (4) ovarian tissue must be demonstrable in the wall of the sac.

This case report of a primary ovarian pregnancy fulfills all the requirements listed by Spiegelberg, but does not add proof to the theory of Viet and Meyer. Microscopic study of the ovarian pregnancy (Fig. 1) shows implantation of the fertilized egg adjacent to (and surrounded by) the corpus luteum, not necessarily demonstrating that the ovum ever left the Graafian follicle. Whether the ovum left the ovary, entered the oviduct, was further matured, fertilized, and then regurgitated back onto the surface of the ovary is unknown. This is Curtis'[1] belief as to implantation in ovarian pregnancy.

Case Report

On Feb. 28, 1954, a 35-year-old nulliparous white woman was admitted to the emergency room of the George Washington University Hospital in acute abdominal distress.

Three hours before admission, while eating breakfast, the patient experienced a sharp "tearing" pain in the right lower quadrant of the abdomen. The pain gradually spread across the lower abdomen and then became generalized abdominally. There was nausea, but no vomiting. There was a desire to, but inability to, defecate. The patient noted weakness as the pain increased. There was no shoulder pain, nor was there any vaginal bleeding.

Four hours after onset of the pain, the patient notified me and she was immediately hospitalized.

Her last menstrual period on Jan. 17, 1954, was ten days late, and lasted only three days. She was overdue ten days on her expected February period. Menses up to this time had been regular every thirty days.

Past history revealed a similar episode three years previously at which time pelvic examination under anesthesia was negative, and dilatation and curettage revealed proliferative endometrium. The patient had been treated conservatively and recovered with no trouble. It was felt at the time that she had had a tubal abortion. Her past history otherwise was negative except for an appendectomy when she was a child.

The patient fainted on admission to the hospital. Physical examination revealed a patient in obvious abdominal pain. The temperature was normal, blood pressure 110/80, pulse 84 and of good quality. The positive findings were moderate involuntary deep rigidity throughout the abdomen, most marked in the right lower quadrant. There was exquisite tenderness to palpation in the right lower quadrant with generalized rebound tenderness referred to the right lower quadrant. Peristalsis was normal.

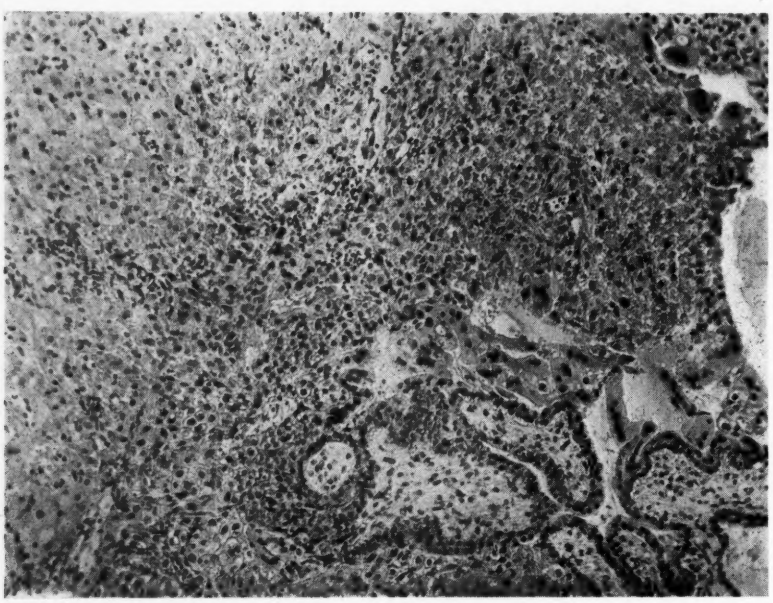

Fig. 1.—Primary ovarian pregnancy. Well-defined chorionic villi are present in lower right center. Layers of cytotrophoblast and plasmotrophoblast may easily be visualized.

Vaginal examination revealed a normal introitus, perineum, and vagina. The cervix was long, firm, and pink. There were several drops of dark blood at the external os. Movement of the cervix elicited severe pain in right lower quadrant. Bimanual examination was unsatisfactory because of pain and rigidity.

The posterior fornix was infiltrated with 1 per cent procaine and a cul-de-sac puncture was performed with a 3 inch No. 15 needle. A small amount of nonclotting, watery blood was removed.

Laboratory findings were: hemoglobin 12.4 Gm., hematocrit 39, white cell count 27,500 with 87 per cent neutrophils and 13 per cent lymphocytes. The urinalysis was negative.

The patient was immediately scheduled for laparotomy with a preoperative diagnosis of ruptured right tubal pregnancy.

Laparotomy revealed the peritoneal cavity to be filled with 500 to 600 c.c. of fresh and clotted blood. The uterus was of normal size and shape. Both tubes were bound down posteriorly by light adhesions, but were normal otherwise. The right ovary showed a raised circular area approximately 2 cm. in diameter which was bleeding steadily. This raised area consisted of friable, spongy, yellow and dark red tissue which separated easily from the underlying normal ovarian tissue. Hemostasis was secured by several interrupted figure-of-eight sutures in the bleeding ovarian tissue. The ovary was not removed or otherwise disturbed except for the removal of the products of conception.

The patient had an uneventful postoperative course. She passed a decidual cast on the second postoperative day.

Summary

A case of primary ovarian pregnancy is described and added to the small number of authentic cases already reported. This pregnancy progressed only six or eight weeks, spontaneously ruptured, and produced a hemoperitoneum. Surgical treatment was conservative, with preservation of the affected ovary and extirpation only of the products of conception and the adjacent corpus luteum.

I wish to thank Mr. J. Frank Delaney of the George Washington University Department of Pathology for the excellent photomicrograph illustrating this paper.

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TWO CASES OF THROMBOCYTOPENIA DURING PREGNANCY TREATED WITH SPLENECTOMY

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THE occurrence of thrombocytopenic purpura in association with pregnancy is fortunately rare. Wintrobe cites 44 cases of thrombocytopenia during pregnancy with maternal mortality in 26. Only 15 infants survived and seven of these showed signs of purpura. Other authors also stress the high maternal and fetal mortality.

Spontaneous hemorrhage from mucous membranes, associated with a reduced number of platelets, prolonged bleeding time, and normal clotting time, is diagnostic of the disease. The usual course is extremely variable, and treatment is difficult to evaluate. Castle states that splenectomy is indicated, but only two-thirds of the patients so treated will be cured.

The following two case reports illustrate the disease:

Mrs. S. S., aged 25 years, was first seen Sept. 15, 1948, her last menses having occurred July 13, 1948. The uterus was the size of a normal two months' pregnancy. She had had an appendectomy in 1932 and a normal delivery in 1945. The patient gave a history of mild nosebleeds and bruising easily for as long as she could remember. Except for scant vaginal bleeding at ten weeks' gestation, her prenatal course was normal until the end of the sixth month. On Jan. 20, 1949, her local physician packed her nose twice to control severe hemorrhage. Gross hematuria was also noted. I saw the patient soon thereafter and found ecchymoses of both forearms and the soft palate. The platelet count was only 20,000 per cubic millimeter, with bleeding time of over 15 minutes. The patient was hospitalized with a diagnosis of thrombocytopenia, and a smear of the sternal bone marrow showed many megakaryocytes. The significant finding indicated that the production of platelets (megakaryocytes are the precursor) was adequate but that some organ, considered to be the spleen, was destroying them. Following transfusion of 2 pints of whole blood, splenectomy was performed on Jan. 24, 1949, and the patient made an uneventful recovery (Table I). Three weeks later, however, she had a mild recurrent purpura which responded to Pyribenzamine and a nonallergic diet. On April 28, 1949, at term, she delivered a normal female infant. There was no excessive bleeding. Except for a mild aplastic type of anemia following excessive ingestion of Alka-Seltzer in 1951, the patient and child have been well.

TABLE I. PATIENT S. S.

DATE	R.B.C./MM.^{3}	PLATELETS/MM.^{3}	BLEEDING TIME (MINUTES)
Adm. 1/20/49	3.70 million	20,000	Over 15
1/21/49	2 transfusions	38,000	12
1/24/49	Splenectomy	24,000	
1/26/49		38,000	
1/28/49	3.76 million	56,000	3½
2/ 2/49		392,000	

Mrs. E. K., aged 35 years, gravida 0, was first seen Feb. 28, 1951, her last menses having occurred Dec. 28, 1950. She noticed scant vaginal bleeding on Jan. 21 and again Jan. 29. Her past history was negative. The uterus was the size of a normal six weeks' intrauterine pregnancy. Soon thereafter she developed a "sore throat" and was treated by her family physician. Two days later, however, her throat was worse and I found the soft palate and pharynx covered with bright confluent petechiae. A platelet count was 97,000 per cubic millimeter. She refused hospitalization until four days later, on May 10, 1951, when a platelet count was 22,200 per cubic millimeter and the bleeding time was over 16 minutes. A smear of sternal bone marrow showed many megakaryocytes and thrombocytopenic purpura with early pregnancy was diagnosed. After transfusion with whole blood, splenectomy was performed and the patient made an uneventful recovery (Table II). The platelets rapidly rose to normal. On Oct. 14, 1951, at term, she delivered a normal female that weighed 6 pounds, 13 ounces. No excessive bleeding was encountered. When seen recently both mother and child were well.

TABLE II. PATIENT E. K.

DATE	R.B.C./MM.^{3}	HEMOGLOBIN (%)	PLATELETS/MM.^{3}	BLEEDING TIME (MINUTES)
Adm. 3/10/51	3.73 million	73	22,200	Over 16
3/11/51	Splenectomy and transfusion		11,040	
3/12/51			100,600	3½
3/13/51	3.20 million	64	195,800	
3/15/51	Transfusion		219,090	
3/17/51			436,000	

Summary

1. Two cases of thrombocytopenic purpura during pregnancy are reported.

2. Both patients had splenectomy, one at three months', the other at six months' gestation.

3. Both patients went to term and delivered normal infants.

AN ABRASIVE ENDOMETRIAL CYTOLOGIC BRUSH*

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THE purpose of this communication is to describe an instrument for obtaining specimens for cytologic examination from the endocervix, the endometrial cavity, the urinary bladder, and the other body cavities.

The instrument consists of a specially designed brush, a brush holder, and a shield.

The brush has a twisted, rust-proof wire handle (Fig. 1) approximately 26 cm. long and of such size as to render it flexible and easy to insert into the brush holder (Fig. 2). The brush itself consists of a group of plastic or natural bristles of suitable stiffness, approximately 5 cm. long by 0.25 cm. in diameter. The end of the brush is turned over so as to (1) prevent trauma from the sharp wire end, and (2) present bristles clear to the end of the brush.

The brush holder consists of a graduated hollow tube (Fig. 2) approximately 15 cm. long and approximately 0.3 cm. in diameter, with a polygonal handle (Fig. 3) at one end and a clamping device or chuck (Fig. 4), which also has a polygonal head. The chuck is drilled and split so that when screwed into the previously described handle it grips the wire stem of the brush firmly.

The shield (Fig. 6) consists of a graduated tube 23.5 cm. long by 0.4 cm. in diameter, with one end bent up and rounded for ease of insertion and open for the passage of the abrasive brush. *The diameter of the distal end is the same as that of the average uterine sound.* The proximal end consists of a knurled head with a bayonet lock for use in attaching a Luer syringe or other commonly used aspirating apparatus. The brush is inserted through this. Mounted on the shield is an adjustable stop with a captive screw (Fig. 5) useful in regulating the depth of insertion of the shield into the uterine or other cavities. There is also an adjustable arrangement (Fig. 7) mounted on the shield, containing an upright over which one ring of a Kahn's forceps, towel clamp, or other suitable instrument may be attached for holding the shield firm while the brush is being used. Fig. 8 shows the instrument ready for use on withdrawal of the brush into the shield.

In use, the stem or wire handle of the brush is slipped through the tube of the brush holder until it reaches the bottom of the chuck, after which a single turn of the chuck with the fingers clamps (or releases) the brush as desired. The abrasive brush, in its holder, firmly gripped by the chuck, is then placed into the shield. After the cervix is exposed, the anterior lip is grasped with a Kahn's forceps or other suitable instrument and the shield with the brush is inserted through the internal os. The brush is then withdrawn into the shield and the brush with shield removed. The brush is again pushed out of the distal end of the shield and smears prepared, following which the brush is discarded.

Comment

While present methods of diagnosis of cancer of the cervix give a high percentage of accuracy, yet the percentage of accuracy is not so high in other body cavities. The abrasive brush here described is so flexible, so obviously

*Presented at the Staff Conference, The Margaret Sanger Research Bureau, Jan. 22, 1954.

harmless, that it can be used very effectively in certain cavities and certain parts of the body which, with present methods, lend themselves to limited investigation only.

Despite the present-day emphasis on early cancer diagnosis, it is clearly impractical and unreasonable to recommend a dilatation and curettage in the case of every slight departure from the normal cycle. Furthermore, if the irregularity continues, despite a dilatation and curettage which proved negative, it is inadvisable to recommend or resort to repeated curettages.

With the use of the abrasive brush, one may perform repeated cytologic testing, with minimum cost, discomfort, or fear to the patient, and minimum effort on the part of the physician. In addition, and what is especially important in the emotional, apprehensive, neurotic, or cancerophobic patient, the simplicity of the procedure permits the procuring of the specimen without the patient's becoming aware of the purpose of the procedure.

FIGURE 1

FIGURE 2 FIGURE 3 FIGURE 4

FIGURE 5 FIGURE 6 FIGURE 7

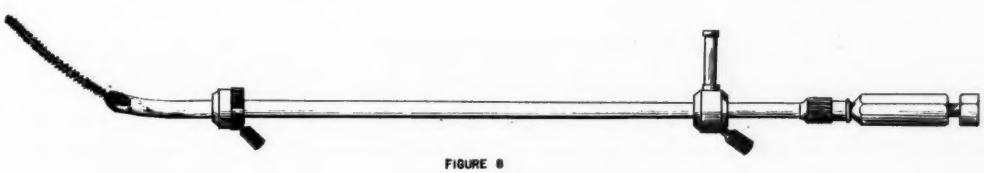

FIGURE 8

The abrasive brush is inexpensive and disposable. Its use will eliminate many curettages, thus overcoming the objections of those who believe that curettages spread the disease. Furthermore, the shield can be used as a uterine sound, a urinary catheter, and a cannula for introducing gas or radiopaque material into the uterine cavity.

Summary

1. A simple abrasive cytologic brush is described, useful in obtaining specimens from the uterine cavity for cytologic examination.

2. Abrasive cytologic brushes and devices are now in process of preparation*† to adapt the principle of the abrasive brush for use in obtaining specimens from many other body cavities and will be described in another communication.

Grateful acknowledgment is accorded to Dr. M. J. Kopac, Professor of Biology at New York University, and to his associate, Mr. Jack Harris, Consultant on instrumentation, Washington Square College, New York University, and Consultant on instrumentation at Cytologic Institute for Cancer Research, New York City, for cooperation in the development and construction of these instruments, and to Mr. Ira Herlzberg of the H. Herlzberg & Sons Brush Company, New York City, for his generous cooperation in developing and supplying the many types of brushes used in the development of these instruments.

*Patents applied for.

†Abrasive devices made of rubber and various other compounds of special design are in the process of experimentation and development. Results will be reported at a later date.

Department of Reviews and Abstracts

EDITED BY LOUIS M. HELLMAN, M.D., BROOKLYN, N. Y.

Selected Abstracts*

Southern Medical Journal

Vol. 47, No. 1, January, 1954.

Word, Buford: Pitfalls of Uterine Curettage, p. 38.

Uterine curettage is the most frequent operation performed in general hospitals throughout the country with the exception of tonsillectomy. There are many errors of omission and commission incident to uterine curettage. This is an analysis of 3,632 cases. The uterus was perforated 40 times. Nineteen of these patients were postmenopausal, 11 had uterine malignancies, 5 were postabortal, and 5 were premenopausal. A small, sharp curette perforated the uterus 20 times and cervical dilators 20 times. The Goodell dilator was the worst offender. If perforation occurs and no tissue is obtained, two weeks should elapse before repeat curettage. Hysterectomy is indicated after accidental perforation only if there is evidence of intra-abdominal bleeding or if it is thought malignant endometrial cells have been pushed into the abdominal cavity. The bowel was grasped in 2 of the 40 perforations but no injury resulted. Hysterectomy was performed in 178 instances immediately after curettage. In 7 patients unrecognized endometrial polyps were found. In only 727 of these 3,632 patients was pelvic examination performed coincidentally with curettage. Examples of serious diagnostic errors as a result of this omission are given. Other pitfalls noted were the administration of radium for incomplete abortion, failure to remove cervical tissue, and unnecessary hysterectomy following perforation.

A safe technique for dilatation and curettage is described.

STEWART A. FISH, M.D.

Montgomery, Thaddeus L.: Cancer Diagnosis in Obstetrics, p. 47.

Because of the relatively long and intimate contact with patients during pregnancy, the obstetrician is in a unique position to diagnose malignant disease seen in association with pregnancy. Cancer in the woman of the reproductive age group is relatively infrequent, but when it does occur the hormone stimulus of pregnancy accelerates the growth and increases the seriousness of the disease. The most common errors are seen in the diagnosis of cervical and breast carcinoma. In order to avoid this, an adequate examination of the cervix with smears and biopsy is recommended. By proper education of the pregnant patient, many individuals may be made aware of the significance of irregular bleeding and other signs of genital cancer, which pays dividends long after their reproductive life is over. Breast lesions are often obscured by the hypertrophy and engorgement of pregnancy and lactation. No breast mass should be ignored or dismissed as inflammatory unless it responds immediately to medical therapy. Complete careful examination of the breasts and cervix post partum is mandatory.

STEWART A. FISH, M.D.

*Titles preceded by an asterisk are abstracted below.

Vol. 47, No. 3, March, 1954.

Byrd, Benjamin F., Jr., and McGanity, W. J.: The Effect of Pregnancy on the Clinical Course of Malignant Melanoma, p. 196.

Tumors arising from melanoblasts are responsive to hormone stimulation. This has been shown to occur in mice and is evidenced by the fact that malignant changes occur rapidly in some previously "benign" moles in children when puberty is reached. Moles are also seen to enlarge rapidly with pregnancy and regress in the postpartum period. The authors suggest that ACTH from the placenta may stimulate melanoblastic activity.

Should malignant melanoma be diagnosed in pregnancy, radical surgical cure (wide local excision and regional node dissection) must be attempted without regard to the coexisting pregnancy. Termination of pregnancy before apparent spread has taken place may prevent or delay metastases. There is apparently little benefit in this procedure when metastases have occurred.

Any woman who has had a malignant melanoma should be advised of the grave risk of pregnancy for fear it may produce "recrudescence" of the tumor. The authors believe the risk of pregnancy in this group is great enough to warrant sterilization.

Two cases are reported. One patient had a pigmented lesion for nine years which enlarged with each of four pregnancies and then regressed post partum. With the fifth pregnancy the lesion was excised widely and malignant melanoma diagnosed. She had no recurrence eight months postoperatively. The second patient had a malignant melanoma excised in the second trimester of her fourth pregnancy. Three years later during her fifth pregnancy she was found to have widespread metastases including massive placental metastases. The fetus died 24 hours after delivery and the mother died 3 weeks later.

STEWART A. FISH, M.D.

Vol. 47, No. 4, April, 1954.

Palumbo, Leonard, Jr.: Primary Carcinoma of the Vagina, p. 356.

The incidence of primary carcinoma of the vagina varies from 0.4 to 2.6 per cent of all female genital cancers. The average age incidence is 55 years, but 5 cases have been reported in infants between the ages of 8 and 21 months. It is also seen in adolescence and pregnancy. Cytologic studies probably do not increase the incidence of early diagnosis. The majority of the symptoms are due to local necrosis and sloughing. Histologically, 90 to 97 per cent are squamous and when the occasional diagnosis of adenocarcinoma is made, the possibility of a metastatic lesion must be ruled out. The most common location for this lesion is on the upper one-third of the posterior vaginal wall. Local spread is followed by involvement of the parametrial, hypogastric, and iliac nodes if the lesion is in the upper two-thirds of the vagina. In the lower one-third, the femoral and inguinal areas are the site of primary nodal metastases.

Treatment is basically dependent on radiation. There is no unanimity of opinion on the optimum dosage, technique, duration, and frequency of this type of therapy. Extreme

radical surgical excision has been attempted with equivocal results. The extensiveness of local infiltration of the lesion does not have the same prognostic significance as it has in cervical cancer. Tabulated results from many sources indicate a total five-year salvage of 12.3 to 21.6 per cent. There has been no improvement in cure rate in the past 20 years, but perhaps in the future combined radiation and surgical therapy may improve the outlook for cure of this disease.

STEWART A. FISH, M.D.

Vol. 47, No. 5, May, 1954.

Vogt, William H., Jr., and Ritter, Hubert A.: Fetal Salvage: A Comparative Study of Two Five-Year Periods, p. 464.

*Donnelly, James F.: Fetal Loss in Relation to Maternal Mortality, p. 464.

Donnelly, James F.: Fetal Loss in Relation to Maternal Mortality, p. 464.

One thousand maternal deaths which occurred in North Carolina between 1946 and 1951 were analyzed. Of these, 844 were considered directly due to complications of pregnancy. Only 41 per cent (338) of conceptions in these women resulted in living infants that survived the neonatal period. Five hundred six of the fetuses were lost. The most common cause of maternal death was toxemia. Two hundred sixty-four patients died, with a fetal loss of 149 infants (due largely to prematurity) and a salvage of 115 pregnancies. The largest single contributing factor noted in the toxic group of patients was inadequate prenatal care due to the apathy and ignorance of the patients. Failure to be hospitalized early was also implicated.

Hemorrhage accounted for 259 deaths, making it the second highest cause of maternal mortality. There were 49 deaths due to ectopic pregnancy and abortion. The remainder were due to placenta previa (25), premature separation of the placenta (53), postpartum uterine atony (90), ruptured uterus (27) and miscellaneous causes (15). The fetal wastage was 168 and fetal salvage 91. Only 81 of the patients who died of hemorrhage received blood transfusions, and less than 10 per cent of transfused individuals received adequate blood replacement. The third most common cause of maternal death, pulmonary embolism, accounted for 74 maternal deaths and 44 fetal deaths. Thirty pregnancies of these mothers were saved. Infection caused 73 maternal deaths, half of which were related to criminal abortion. Fetal salvage was said to be 54 per cent. There were 46 deaths due to heart failure secondary to rheumatic heart disease. The fetal salvage was 27 infants and the fetal loss 19. Anesthesia was the cause of 25 deaths, 9 each for spinal and ether anesthesia. There were 2 deaths from chloroform and 2 from Pentothal. Cyclopropane, curare, and local anesthesia each accounted for one maternal death. Other obstetrical complications, such as tuberculosis, an acute condition of the abdomen requiring surgery, acute yellow atrophy of the liver, etc., were diagnosed in the remaining 103 maternal deaths. A 45 per cent fetal salvage was obtained in this group.

A discussion of methods of decreasing fetal and maternal mortality follows these statistical data.

STEWART A. FISH, M.D.

Vol. 47, No. 6, June, 1954.

*Sutherland, C. G., Brown, W. D., Atkinson, J. C., and Birmingham, R. T.: Experimental Studies on the Repair of Ureteral Injuries, p. 525.

*Douglas, R. Gordon, and Birnbaum, Stanley J.: Urological Complications Following Radiological and Surgical Treatment of Carcinoma of Cervix, p. 559.

Sutherland, C. G., Brown, W. D., Atkinson, J. C., and Birmingham, R. T.: Experimental Studies on the Repair of Ureteral Injuries, p. 525.

The incidence of recognized ureteral injury during gynecologic surgery is about 3 per cent. It is impossible to determine the rate of occurrence of occult injury. Most

efforts at repair of these injuries are not entirely satisfactory because of the resulting fibrosis and stenosis at the site of repair. If excess scar formation could be prevented at the site of ureteral anastomosis many complications could be avoided. Three different experimental approaches to this problem were selected:

1. Cortisone was administered to dogs with ureterointestinal anastomoses. The animals were sacrificed at 30 to 144 days. No significant reduction in fibrosis at the anastomotic site was found.

2. In an effort to determine the role of suture material in the production of inflammatory reaction with subsequent stenosis, an experiment on ureteral regeneration in dogs was performed. A one-inch segment of lower ureter was excised and a polyethylene catheter used to bridge the gap. Catheters were left in place for 6 to 27 days. It was found that 11 days was the minimum time for epithelial regeneration to occur and 23 days of intubation was the minimal time necessary to avoid stenosis.

3. Normal dog ureter was severed and loosely approximated, without sutures, over a polyethylene tube. Fourteen days or more of intubation permitted epithelial regeneration with minimal scar formation.

It is suggested that this last method might be useful in reducing the incidence of ureteral stricture following anastomosis.

STEWART A. FISH, M.D.

Douglas, R. Gordon, and Birnbaum, Stanley J.: Urological Complications Following Radiological and Surgical Treatment of Carcinoma of Cervix, p. 559.

In recognition of the possible role of radical pelvic surgery in the treatment of cervical carcinoma, an analysis of complications seen in 64 patients treated by surgery with or without preoperative radiation is presented. Urological complications are considered in detail and compared with similar complications reported by Meigs, Peterson, and Hornbrook and by Donnelly and Caldwell and Kelso. The details of the plan of therapy used for primary cervical carcinoma at the New York Lying-In Hospital are described. Ninety per cent of the cases treated were Stage I or II (League of Nations), and the remainder were Stage III and IV. Preoperative radiation was given to 86 per cent of the patients, and the remaining 14 per cent were treated solely by radical surgery. Both immediate and delayed postoperative urinary complications occurred. All patients developed transient bladder atony that persisted for two to eight weeks. To obviate this, an indwelling catheter was used for one week, followed by tidal drainage for the second postoperative week. All patients had gross hematuria for two to five days postoperatively. Chronic bladder dysfunction with alteration in capacity, incontinence, or bladder deformity occurred in 13 per cent of the patients. Urinary tract infection developed in 84 per cent of the patients with 20 per cent of the cases becoming chronic. The chief bacterial offenders in the acute disease were *B. coli, B. aerogenes,* and aerobic or anaerobic nonhemolytic streptococcus. In the chronic infection, the organisms cultured were *B. proteus, B. pyocyaneus* and nonhemolytic streptococcus. Diminished renal function (elevated nonprotein nitrogen, delayed intravenous pyelogram function) occurred in 48 per cent of the patients, but returned to normal in five to seven days. In 13 per cent poor function continued and "silent kidney" developed in several cases. Postoperative hydropic change of the upper urinary tract was present in 55 per cent of the patients and was attributed to periureteral edema. These changes persisted in 30 per cent of the patients operated upon. There were 6 instances (9 per cent) of urinary tract fistula of various types and, of these, 4 required bilateral nephrostomy. Of the remaining 2 patients, one had a nephrectomy and one a cutaneous ureterostomy. In addition to urinary tract complications, persistent distal edema was seen in 9 per cent of the series, pelvic abscess in 6 per cent, rectovaginal fistula in 5 per cent, and thrombophlebitis in 5 per cent of the patients. No emboli occurred. Three per cent of the wounds disrupted and 3 per cent of the patients suffered reactive depression which required psychiatric care. Other miscellaneous postoperative complications were intestinal obstruction, atelectasis, vaginal vault hemor-

rhage, radial nerve palsy, prolonged hypotension, and pulmonary edema probably due to electrolyte imbalance. One death occurred from homologous serum jaundice. Eight other deaths have occurred, chiefly from recurrent carcinoma.

A discussion of postoperative complications with special reference to etiology and prevention follows the statistical data. Definite conclusions as to the relative value of surgery in the treatment of cervical carcinoma cannot be made until a larger series is collected.

STEWART A. FISH, M.D.

Deutsche medizinische Wochenschrift

Vol. 79, No. 12, March, 1954.

Noack, H.: How Can We Combat Perinatal Mortality? p. 461.

In a study of perinatal mortality in over 50,000 births, it is shown that prematurity accounts for over one-half of the uncorrected mortality of 4.9 per cent. The solution of the problem of prematurity can be found only in good prenatal care and, particularly, in proper nutrition. Toxemias of pregnancy must be recognized and treated early. Particular attention should be paid to those complications which, with proper treatment, will give a good fetal result but are actually responsible for many cases of infant loss. These are complications due to abnormalities of the umbilical cord, placenta previa, abnormal presentations, contracted pelvis, and uterine inertia. Liberalization of fetal indications for cesarean section should be considered. The prevention of the injudicious application of this method demands a great refinement in obstetrical judgment. The author considers a section rate of 3 per cent to be proper.

W. F. TAUBER, M.D.

Vol. 79, No. 17, April, 1954.

Vossschulte, K.: On the Pathology of Portal Hypertension and Its Treatment. Conclusion, p. 712.

Roemer, G. B.: Etiology, Epidemiology, and Prophylaxis of Virus Hepatitis, p. 719.

Krauss, H., Reindell, H., Klepzig, H., Musshoff, K., and Stegmann, H.: Commissurotomy in Pregnancy, p. 690.

The authors present a case of mitral stenosis complicating pregnancy. The patient went into intractable failure in the fifth month. She underwent commissurotomy with the pregnancy left undisturbed. A good clinical result was obtained. A review of the limited literature on the subject is presented.

W. F. TAUBER, M.D.

Vol. 79, No. 18, April, 1954.

Lodenkaemper, H., and Stienen, G.: Contribution to the Problem of Aging, p. 739.

Sturm, A.: Adrenal Control in Relation to the Autonomic Nervous System. Part I, p. 741.

Betzler, H. J.: On the Recognition and Treatment of Carcinoma of the Colon, p. 750.

Schattman, K.: Critique of the Paper Entitled, "On a Simple Quantitative Determination of Free Isonicotinic Acid Hydrazide in Urine," by Smolarek, W., and Stahl, R., p. 758.

Meyer zu Schwabedissen, O.: Critique of the Paper Entitled, "On the Determination of Isonicotinic Acid in the Urine. Conclusion," by Smolarek, W., and Stahl, R., p. 759.

Vol. 79, No. 19, May, 1954.

The Treatment of Cerebral Hemorrhage With the Sympatholytic Agent Opilon, p. 776.

Balzer, E., and Baeumer, A.: On the Course of the Bilirubin Level in the Blood in Various Types of Jaundice, p. 779.

Strum, A.: Pituitary-Adrenal Control in Relation to the Autonomic Nervous System. Conclusion, p. 782.

Sauerbrei, H. U.: Some Cases of Meningococcal Infections With Waterhouse-Friderichsen Syndrome, p. 785.

Kranz, H.: The Determination of Clotting Values in Control of Dicumarol Therapy, p. 788.

Forensic Obstetrics: Naujoks, H.: Who Perforated the Uterus? p. 789.

Editorial survey: High voltage therapy, p. 790.

Vol. 79, No. 20, May, 1954.

Berg, H. H.: Thromboembolic Phenomena and Diet, p. 801.

Kalk, H., and Wildhirt, E.: Contribution to the Clinical Picture of Periarteritis Nodosa, p. 803.

*Frangenheim, H., and Schenk, G.: Morphological Observations on the Treatment of Tuberculous Endometritis With Conteben® and Neoteben®, p. 807.

Broglie, M.: The Therapy of Inflammatory Arthritides, p. 816.

Frangenheim, H., and Schenk, G.: Morphological Observations on the Treatment of Tuberculous Endometritis With Conteben® and Neoteben®, p. 807.

The authors have studied histologically the effect of Conteben and Neoteben together with PAS in 19 cases of endometrial tuberculosis. They demonstrated that the agents are not only bacteriostatic, but actually enhance positive healing processes with fibrotic lesions as an end stage after about three to four months of treatment.

W. F. TAUBER, M.D.

Vol. 79, No. 21, May, 1954.

Janz, D., and Bahner, F.: Medicinal Treatment of Obesity With a New Hydantoid, p. 846.

Adam, W., and Wittig, R.: Is External Application of Isopropyl Alcohol Innocuous? p. 849.

Vol. 79, No. 22, May, 1954.

Kleine, H. O.: Vitamin A Therapy in Nervous Premenstrual Complaints, p. 879.

One hundred cases of premenstrual tension treated with vitamin A are discussed. Good results are reported. Literature is quoted to show that thyroid activity is increased in the second half of the menstrual cycle and that vitamin A is helpful on a theoretical basis because: (a) there is a relatively higher need, and (b) this vitamin has a tendency to depress thyroid activity.

W. F. TAUBER, M.D.

Doering, G. K.: The Reaction to Sensory Stimuli in the Course of the Menstrual Cycle, p. 885.

Experimental work was done to test changes in reaction time throughout the menstrual cycle. Results on six healthy subjects showed no fluctuation through the cycle.

W. F. TAUBER, M.D.

Clauss, J.: Culdoscopy and Sterility, p. 886.

The author states that determination of tubal patency is the most important single fact to be established in the female partner in sterility work. He feels that intrauterine instillation of aqueous dye together with culdoscopy is the best method at hand. This permits examination of the tubes under direct vision. At the same time various abnormalities can be recognized or ruled out. The main advantage of this method lies in avoiding exposure of the ovaries to x-radiation. Since this technique is not without dangers, its use should be limited to expert hands.

W. F. TAUBER, M.D.

Brasche, K. H.: Experiences With the Houssay-Toad Test for Pregnancy, p. 893.

The authors evaluate 687 tests for pregnancy with the toad. There were 1.3 per cent false negatives and no false positives in their series. These results are superior to those of every other pregnancy test except the Aschheim-Zondek, with the great advantage that test results can be obtained in one to three hours. Directions are given for the care of the test animals.

W. F. TAUBER, M.D.

Vol. 79, No. 23, June, 1954.

Vol. 79, No. 24, June, 1954.

vestigation of Agents Acting on Blood Vessels, p. 944.

Laudahn, G.: On the Differential Diagnosis of Hepatitis and Obstructive Jaundice, p. 948.

Fahrlaender, H., and Klingler, M.: Periarteritis Nodosa and the Nervous System, p. 952.

Becker, J.: On Temporary Suppression of Sympathetic Activity, p. 972.

Perlick, E.: Marcumar and Intermittent Anticoagulant Therapy, p. 980.

Harrer, G.: On the Biologic Activity of Brain Hydrolysates, p. 983.

The Journal of Pediatrics

Vol. 44, May, 1954.

*Krugman, Saul, and Ward, Robert: The Rubella Problem, p. 489.

Hartmann, Alexis F., McCoy, Ernest E., Swarm, Pauline A., and Nakasato, Doris I.: Further Observations on the Metabolism of Galactose in Infants and Children, p. 499.

Rugh, Roberts, and Booth, Elisabeth: Modification of Maternal and Fetal Effects of Radioiodine by Pretreatment of the Mother, p. 516.

*Lee, Henry F.: A Rocking Bed Respirator for Use With Premature Infants in Incubators, p. 570.

Krugman, Saul, and Ward, Robert: The Rubella Problem, p. 489.

This is a fine review of the present status of the disease. Information is presented on experimental rubella and on the effect of gamma globulin. A section of the paper deals with the risk of congenital malformations when the disease attacks the pregnant woman. The authors' data suggest that the incidence of such blighted pregnancies is between 10 and 20 per cent when the disease is present during the first trimester.

SCHUYLER G. KOHL, M.D.

Lee, Henry F.: A Rocking Bed Respirator for Use With Premature Infants in Incubators, p. 570.

This communication introduces a small rocker similar to the standard-sized one used in many delivery rooms. The advantage of this "machine" is that it is small enough to be placed inside an Isolette. Thus if one desires to use a "rocker" on a premature infant being treated in an incubator, he can do so.

SCHUYLER G. KOHL, M.D.

Irish Journal of Medical Science

May, 1954, Sixth Series, No. 341.

*Geoghegan, A. P., and Geoghegan, F.: Accidental Hemorrhage: Abruptio Placentae, p. 189.

Nolan, M. M.: Obstetrical Problems in Nigeria, p. 205.

*Browne, Alan D. H.: Treatment of Deep Venous Thrombosis in the Puerperium, p. 212.

Geoghegan, A. P., and Geoghegan, F.: Accidental Haemorrhage: Abruptio Placentae, p. 189.

The authors give the usual possible etiological states associated with abruptio placentae. In addition they state that "iron deficiency anaemia during pregnancy may be a predisposing factor." No substantiating evidence is presented.

A concise review of the relationship of placental separation and afibrinogenemia is presented, along with a detailed outline for the treatment of this complication.

Two hundred thirty-four cases of placental separation are reported from the National Maternity Hospital of Dublin (1950-1952). There were 3 maternal deaths in this series. The deaths were thought to be due to eclampsia, cortical necrosis, and hemorrhage,

respectively. The deaths occurred among the 64 cases that were classified as severe. Seven patients were treated by cesarean section; all were in the group of severe cases except one.

The authors have presented a most worth-while review of the subject in addition to their own experience.

SCHUYLER G. KOHL, M.D.

Browne, Alan D. H.: The Treatment of Deep Venous Thrombosis in the Puerperium, p. 212.

Dr. Browne reports that there have been six cases of deep venous thrombosis in the puerperium at the Rotunda during the period 1951-1953. All the cases have been treated by unilateral paravertebral block. The treatment has been uniformly successful.

The procedure used at the Rotunda is given in full detail. The author discusses this method of therapy as opposed to the use of anticoagulants. In doing so he makes a good case for paravertebral block.

This well-written article is highly recommended.

SCHUYLER G. KOHL, M.D.

New York State Journal of Medicine

Vol. 54, No. 11, June 1, 1954.

*Smiley, L. V.: Stress Incontinence in Women, p. 1609.

*Lavell, T. E., Knauer, G., Jr., and Winterhalter, C. McN.: Evaluation of Stigmonene Bromide as a Corroborative Test in Early Pregnancy, p. 1642.

Smiley, L. V.: Stress Incontinence in Women, p. 1609.

The etiology of stress incontinence in the female has been studied in recent years from the anatomic and physiologic standpoint. Kennedy believes that relaxation of the "muscle of micturition" allows the normally circular bladder sphincter to assume an elliptic shape with its long axis in the sagittal plane. With stress, the sphincter is then unable to compress the urethra, and urine is free to run out of the bladder. Folsom, Powell, Hencz, and Huffman have all studied the posterior urethra and implicate this structure in stress incontinence. The author believes that the periurethral glands described by Folsom may become cystic and the surrounding mucosa hyperplastic, thus distorting the bladder neck and proximal urethra. This distortion of the bladder neck prevents the sphincter mechanism from functioning properly. In this condition there may be no incontinence with normal intravesical pressures. Under stress, however, usually associated with sudden increase in intra-abdominal pressure, urine leaks through the distorted sphincter. The author believes treatment of this condition is simple and his basic approach is fulguration of the cysts and posterior urethra with the electrode of an operating cystoscope. Urinary tract infection and the presence of residual bladder urine are not part of the physical findings accompanying the syndrome the author describes. In many instances both cystocele and changes in the bladder neck coexist. The author reports a series of 17 women who were treated by endoscopic fulguration and notes that the treatment is most effective in those patients in whom no previous pelvic surgery has been attempted and in whom there are no abnormalities of the supports of the urethra and bladder neck. In other instances in which cystocele repair has failed or there has been pelvic surgery, the results are generally less satisfactory.

The author emphasizes that in all cases of stress incontinence bladder observation is mandatory in order to rule out local etiological factors.

STEWART A. FISH, M.D.

Lavell, T. E., Knauer, G., Jr., and Winterhalter, C. McN.: Evaluation of Stigmonene Bromide as a Corroborative Test in Early Pregnancy, p. 1642.

Some investigators believe that hyperemia of the endometrium occurs prior to the onset of the menstrual flow and that this is due to the vasodilating action of acetylcholine

released by estrogen. This phase of menstruation has been shown to be under the control of the parasympathetic nervous system. In some instances, if the vascular response of the endometrium is poor, the endometrium does not become hyperemic and fails to desquamate. It has been suggested that physostigmine-like compounds might overcome this poor vascular response by potentiating the stimulating effect of acetylcholine through inactivation of the enzyme cholinesterase. It has been shown that the administration of a parasympathomimetic or cholinergic compound does not interfere with, or disturb the course of, an existing normal intrauterine pregnancy. If no pregnancy exists, in individuals with simple delayed menstrual periods, administration of cholinergic drugs promptly produces menstrual flow. In instances in which amenorrhea is not due to poor "vascular responsiveness," cholinergic drugs are ineffective. The authors report a series of 77 patients with simple delayed onset of menstruation or with the clinical diagnosis of early pregnancy, in whom a new cholinergic drug was employed. This drug, Stigmonene bromide (1-benzyl-3-[dimethylcarbamyloxy] pyridinium bromide) is a synthetic alkaloid-like salt of the quaternary pyridinium series and acts as an inhibitor of the enzyme cholinesterase. Of the 77 patients treated with 1 mg. of Stigmonene bromide daily for three successive days, vaginal bleeding failed to occur in 69 instances. In all of these patients pregnancy was subsequently confirmed clinically. Of these 69 patients, 2 developed episodes of bleeding, one apparently due to a cervical erosion and the other due to threatened abortion, which was apparently not related to the administration of the drug. The remaining 8 amenorrheic women in this group were not pregnant clinically and in every instance after the administration of the drug uterine bleeding was initiated within 6 to 96 hours after the last injection. An Aschheim-Zondek test (Friedman modification) was performed on each of the 69 gravid women. It was interpreted negative in 10 instances, representing an inaccuracy of 14.5 per cent. In the nonpregnant group the pregnancy test was interpreted incorrectly in two instances.

Stigmonene was administered to an additional group of 21 patients with irregular menses, obesity, gross pelvic pathology, or menopausal amenorrhea. The results were variable and inconclusive. The author agrees with Decker, who believes that if bleeding occurs more than eight days after the administration of the last injection of a cholinergic drug the bleeding is due to some factor unrelated to the drug which was injected.

STEWART A. FISH, M.D.

Correspondence

Single Application of Forceps to Correct Occipitoposterior Position

To the Editors:

The July, 1954, issue of the AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY, a festschrift in honor of Dr. George W. Kosmak, contains an article contributed by Arthur H. Bill, M.D., entitled, "Forceps Delivery." This paper is an excellent presentation of the life-long experience of one of the leaders in clinical obstetrics in America. The article restates[1] Dr. Bill's modification of the Scanzoni forceps operation used in the handling of cases of occipitoposterior position.

Those fortunate enough to have received obstetrical training under Dr. Bill, and to have worked in his clinic many years, have found that this modified Scanzoni maneuver is an ever present help in time of trouble—a relatively simple and safe adjustment that corrects a condition fraught with potential danger.

If the obstetrician has assessed his case carefully, and made sure that there is no disproportion or other contraindication, it is surprising how uniformly the double application of the blades works easily and efficiently. But "nothing in medicine is a hundred per cent." Quite rarely one meets an occiput head which, when turned from, say, right occiput posterior to occiput anterior during the first application of the blades, will insist upon dropping back to a posterior position when the forceps are removed prior to the second application for extraction.

(In the subsequent discussion, we shall consider the right posterior position. That is the more common one; modification of the following directions to apply to left posterior heads will be obvious.)

In these rare cases that refuse to remain anterior after the turning, it has been found possible to carry out the principles of the Scanzoni-Bill maneuver with a single application of the blades, which are put on "upside down." In other words, the forceps are applied so that the handles point almost straight downward. When in place, before any turning, they are, in relation to the mother (not the fetus), in the position they occupy at the end of the turning maneuver in the orthodox Scanzoni operation.

With the head, then, in right occipitoposterior position, the right hand is carried up the left side of the vagina to locate the right ear. The operator's left hand holds the right forceps blade, handle down; reversed, so that the convexity of the pelvic curve is up. This blade is introduced into the vagina on its left side, and slid along the operator's right palm to a position over the ear. The handle is kept well down, at some point between "six o'clock" and "eight o'clock," depending upon the direction of the sagittal suture. The second (left) blade is now applied, also reversed, and the forceps are locked. (In the left occipitoposterior position, the blades must be crossed before locking.)

With the patient's buttocks at the very edge of the table, and with the knees well separated, the tips of the handles, now pointing downward, are swung gently to the (mother's) right and then upward, in a smooth clockwise rotation, keeping them well out from the midline. It is well for the operator to use one hand gently in this turning movement. The other hand is applied to the abdomen above the pubis, in the effort to assist the child's shoulders to rotate as the forceps turn the head anterior.

This rotation must be carried out with the greatest gentleness; the head is just guided around, never forced in the slightest degree. No downward traction is exerted during the

rotation. In fact, sometimes when slight resistance is felt, it is well to push the head back a little. In this way it may be dislodged and made mobile when it has become jammed into the pelvis. We prefer a solid-blade forceps of the Tucker-McLane type. If, in turning, the blades slip around on the head a little, a fenestrated blade is more likely to cut the head or injure the ear.

When the rotation has been carried around until the handles point upward, a check will show that the right occipitoposterior position has been changed into an occipitoanterior one. The blades are slightly relaxed; if there has been any slipping on the head, they may be readjusted. But they are not removed, so the head has no chance to fall back to the posterior position. It will now be seen that the forceps are applied to a head in an anterior position. We have what is really a simple low-forceps delivery of a head in the right occipitoanterior position. The forceps are in the correct position, and they have been applied only once. So go ahead with the extraction!

Summary.—A method is described whereby a single application of forceps blades "upside down" makes possible both the turning and the extraction of a head in the occipitoposterior position. Such a single application prevents the head from falling back to a posterior position after it has been turned anterior.

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OCT. 4, 1954

Reference

1. Bill, Arthur H.: AM. J. OBST. & GYNEC. 9: 342, 1925.

Items

Meeting of American College of Surgeons

A four-day Sectional Meeting of the American College of Surgeons will be held in Cleveland, Ohio, Feb. 21 through 24, 1955, at the Hotels Cleveland and Hollenden.

Two New Study Sections, National Institutes of Health

The Division of Research Grants of the National Institutes of Health will establish two new study sections, one in biophysics and the other in human embryology, on Jan. 1, 1955. Applications for review at the first meetings of the two sections will be accepted up to March 1, 1955.

The Biophysics Study Section will be concerned with the field of molecular biology, the study of living matter at the molecular level, particularly from the standpoint of the disciplines of physics, physical chemistry, colloid chemistry, and protein chemistry. Dr. F. O. Schmidt, of the Massachusetts Institute of Technology, will serve as chairman of the group, and Dr. Irvin Fuhr, of the Division of Research Grants, NIH, as executive secretary.

The Human Embryology and Development Study Section will review research proposals concerned with such problems in human reproduction as infertility, pregnancy and labor, congenital malformations, and the newborn, especially the premature. Dr. Louis Hellman, of the State University of New York, New York City, has been named chairman, and Dr. Elsa O. Keiles, Division of Research Grants, executive secretary.

The establishment of these two new sections will bring the total number of study sections in the Research Grants Division of NIH to nineteen.